

**Norman G. Bowery: A Founding Father of the GABAB
Receptor Research Field: Reflections on His Contribution
(Second Edition)**

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Chapter 15

Norman G. Bowery: A Founding Father of the GABA_B Receptor Research Field – Reflections on His Contribution

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Abstract

This chapter is dedicated to the history of Norman George Bowery and his groundbreaking discovery of GABA_B receptor. This chapter focused on Norman's brilliant career from the beginning, towards his retirement, and to the legacy that he left in the scientific community: that is why Norman is called the "Father of GABA_B receptor." Here are reported the first evidence of GABA_B receptor existence spanning to the pharmacological characterization, and the following development of Norman's own group on GABA_B receptor, and the huge innovation that he brought to the scientific community, because the GABA_B receptor is a major factor in the central nervous system inhibition, therefore when not working properly it is involved in many diseases. The chapter also reports about the collaboration between Norman Bowery and Alessandra Princivalle, who was so honored and fortunate to have the opportunity to work with such an inspirational and worldwide recognized scientist and is now the author of this work. This chapter consider a brief overview of the latest Norman's work, before moving to GlaxoSmithKline, Verona, Italy. This chapter concludes with the greatest recognition to Norman Bowery for being Norman and discovering the GABA_B receptor.

15.1 Norman Bowery

Norman George Bowery (Fig. 15.1; Fig. 15.2) was born in London in 1944. Norman began his career at The National Institute of Medical Research. He then worked at the newly opened CIBA Research Unit (a Swiss company later bought out) at Horsham in Sussex, UK. Norman left CIBA to begin a PhD with Professor David Brown and it was this fundamental work that led to his groundbreaking discovery of the γ -aminobutyric acid (GABA) type-B (GABA_B) receptor. He was then invited to take the Chair of Pharmacology at the prestigious School of Pharmacy in London. He spent successful years in this position. His following appointment was at the University of Birmingham, becoming Chair of Pharmacology, and Head of Division of Neuroscience and it was here in 1998 that I had the fantastic opportunity to start to collaborate with him. Norman came to pick me up at the airport as the friendliest professor I have ever met up to that point in my life. The first impression was then confirmed

in all the following years we worked together and became friends with respective families. Norman demonstrated a very happy, easy, and warm personality, always ready for a good laugh in company. When any problem arose, work or life, he was ready to discuss it and find a solution for it. That was the inspirational man for everybody who met him: collaborators, students at all levels from undergraduates to PhD. Norman was a huge lover of Italy and Italians, and Italian wines, in fact when he left the University of Birmingham he moved to work for GlaxoSmithKline (GSK) in Verona, Italy, before going back to University of Birmingham to deliver pharmacology lectures as Honorary Professor and he did it as a hobby. He was president of the British Pharmacological Society from 1995 to 1997 and from 1999 to 2000.



Figure 15.1 Professor Norman George Bowery FBPhS (1944 - 2016) British pharmacologist.



Figure 15.2 Young Norman Bowery in the laboratory.

15.2 Norman and early evidence of a second type of GABA receptor (1970s - 1982)

Norman started his work on GABA in the seventies during his time in Professor Brown's laboratory, reporting *in vitro* observation of depolarization of sympathetic ganglia induced by gamma-aminobutyric acid (Bowery and Brown 1972). Since then, his interest in the action of GABA and its action in different compartments of the central (CNS) and peripheral (PNS) nervous system never stopped (see PubMed Bowery et al. 1972-1975)

He continued his studies investigating the action of three analogues namely 4-aminotetrolic acid (4-ATA), *trans* 4-aminocrotonic acid (4-ACA), and imidazole-4-acetic acid (IAA) capable of depolarizing the ganglia in a way similar to GABA (Bowery and Jones, 1976). After these analogues he evaluated other compounds including other amino acids (Bowery et al. 1976a) bicyclic phosphorus esters as convulsant (Bowery et al. 1976b). Norman and colleagues also investigated several other aspects of the GABA inhibitory system in ganglia (Bowery and Dray 1976c; Neal and Bowery 1977; Bowery and Dray 1978). In 1978 Norman and his collaborators clarified aspects of isoguvacine, and muscimol analogues acting on GABA receptors in rat ganglia (Bowery et al. 1978). During the following few years Norman and colleagues advanced their studies by using baclofen which identified a new type of GABA receptor (Bowery et al. 1980). In this historic paper in Nature journal, Norman and co-workers

shed light on why GABA affected and reduced the release of H³-noradrenaline in atria, and H³-acetylcholine in preganglionic terminals, and these events were not affected by bicuculline. So, their hypothesis was: there must be a different and separate type of GABA receptor present on nerve terminals. To test this hypothesis, they used three different *in vitro* systems with specific neurotransmitters and measured the release of evoked K⁺. The first were slices from rat cerebellum, in which the release of H³-noradrenaline was measured in three different settings incubated with (i) high KCl (25mM), (ii) baclofen 100μM, and (iii) GABA 100 μM. The same set was used to test the striatum and the release of H³-dopamine; and the frontal cortex and the release of H³-serotonin. All the set of experiments gave the same results: a reduction in released of the tritiated neurotransmitters (Fig. 15.3; Fig. 15.4).

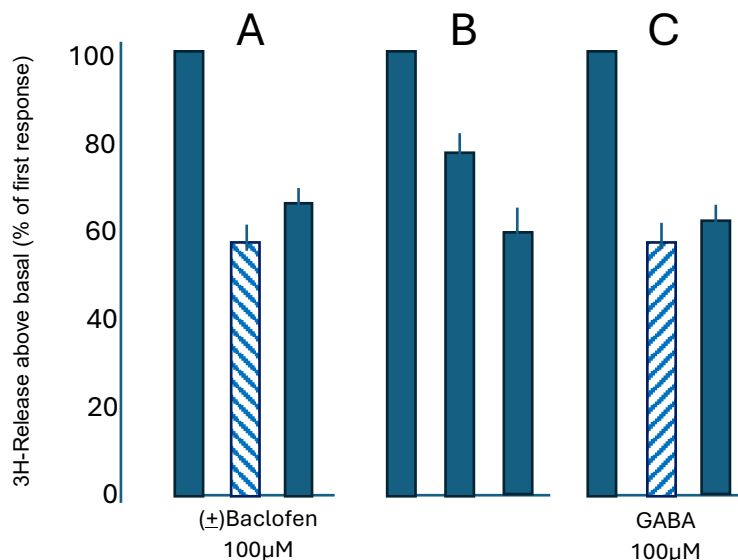


Figure 15.3. Fig. A and C, (±)baclofen (100 μM) and GABA (100 μM), respectively, added 1 min before the second period of superfusion with KCl. Fig. B shows the responses to successive additions of KCl. Figure adapted from Bowery NG, et al. 1980, with permission from Springer Nature.

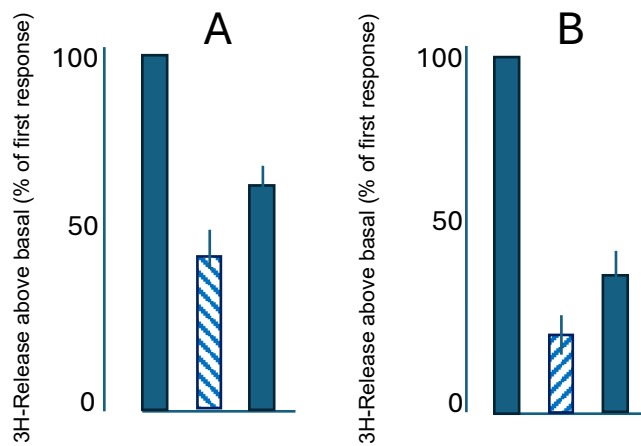


Figure 15.4. Results obtained Depression of K⁺-evoked release of ³H-dopamine (a) and ³H-serotonin (b) by (±)baclofen. Fig. A on the evoked release of ³H-dopamine from striatal slices and Fig. B ³H-serotonin from cortical slices- (B) Figure adapted from Bowery NG, et al. 1980, with permission from Springer Nature.

They also tested other analogues of the GABA, and different concentrations of K⁺ support these findings. The huge breakthrough of a second GABA binding site, or as they call it first “a novel GABA receptor”, was made... YES!!! Hurray!!! This was the birth of GABA_B receptor and Norman Bowery was its absolute father. Norman’s work on this fascinating and exciting novelty continued by further corroboration for the existence of the second GABA binding site. Norman with David Hill performed classical homogenized crude synaptic membranes radioligand binding experiments on rat brain first using H³-baclofen, with different experimental conditions adding different cations to the buffer to check saturability of baclofen. They first set the best conditions for the investigation of the second GABA binding site, and then they used (-) baclofen and GABA as non labelled displacing compounds. They showed that the displacement curves for GABA and (-) baclofen were the same in the same experimental conditions whereas (+) baclofen did not show any displacement (Fig. 15.5). They also tested other GABA type-A (GABA_A) receptor agonists (isoguvacine) and antagonists (bicuculline), and they did not have any effect on the displacement of H³-baclofen (Fig. 15.5).

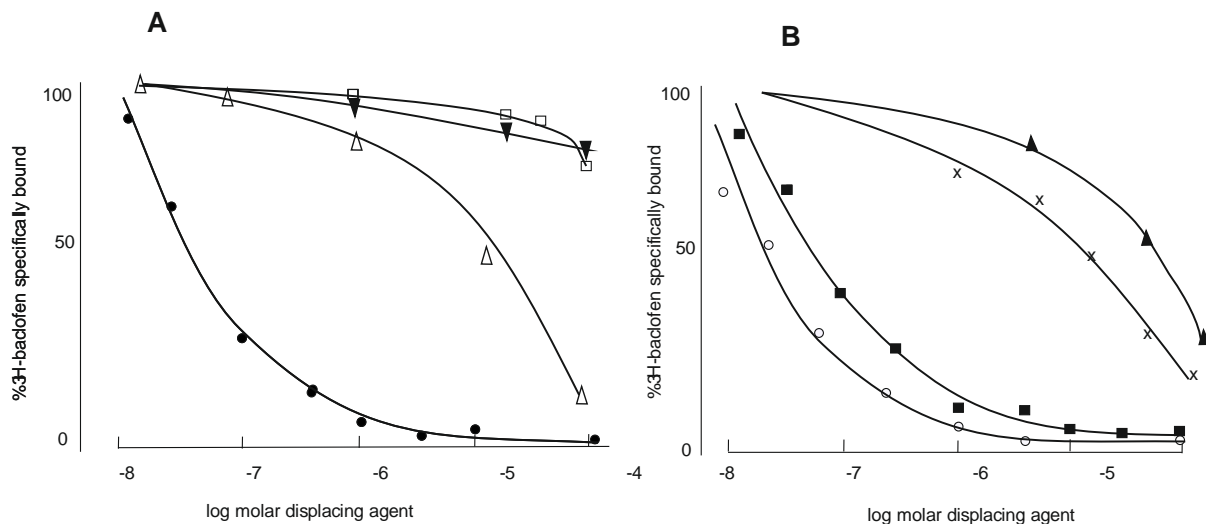


Figure 15.5. Inhibition of (\pm)³H-baclofen binding by GABA-related compounds. Unlabelled analogues at final concentrations between 0.01 and 100 μ M were added to each incubation mixture together with ³H-baclofen (20 nM final concentration). Specific binding was taken as the amount of label displaced by (\pm)baclofen (100 μ M). The amount displaced by individual concentrations of each analogue (log molar, abscissa) is expressed as a percentage of the total displaced by 100 μ M (\pm)baclofen within the same experiment. The data have been separated for clarity. A Shows the effect of GABA (●), muscimol (Δ), isoguvacine (\blacktriangledown) and bicuculline methobromide (\square). B Shows the effects of (-)baclofen (\circ), (\pm)baclofen (\blacksquare), 3-aminopropanesul-phonic acid (x) and (+)baclofen (\blacktriangle). Figure and legend adapted from Hill and Bowery 1981, with permission from Springer Nature.

Finally, to distinguish the two different binding sites Norman and David named GABA_A receptor the original binding site and GABA_B receptor the newly discovered and confirmed binding site. (Hill and Bowery 1981).

Norman and collaborators did it and continue their research on the GABA_B receptor, and a lot of new knowledge emerged quickly (Bowery et al. 1981a; Doble et al. 1981).

Other papers were based on pharmacological techniques which led to the breakthrough of the existence of a GABA receptor which was not the ionotropic one but a metabotropic (Bowery et al. 1981b; Wilkin et al. 1981).

15.3 Norman's studies on the "novel GABA receptor" (1982 - 1992)

Norman and various collaborators continue their studies to localize this novel GABA receptor which they named GABA_B to be distinguished from the benzodiazepine activated ionotropic receptor named GABA_A (Bowery et al. 1983). Norman and his team went on with their studies to gather and advance knowledge about this new receptor: there were a lot of new questions opening at the horizon of this discovery: such as the localization in different nuclei and parts, and physiological pathways of CNS and PNS; as well as the specific cellular and subcellular localization (Bowery et al. 1984; Price et al. 1984; Bristow et al. 1986; Price et

al.1987; Bowery et al.1987). Norman also did other studies on the heterogeneity of GABA_B receptors. Sort of “a preconception” to the molecular characterization of the whole GABA_B multidimer (Bowery et al. 1990), and they were also able to pharmacologically differentiate “subtypes” of GABA_B receptors. Additional studies in Norman's group demonstrated that neuronal degeneration could be induced by tetanus toxin accompanied by a reduction of GABA_A and not GABA_B sites in rat hippocampus (Bagetta et al. 1990), a further corroboration for the two different GABA receptors. Most importantly from the whole body of evidence emerged that a new versatile drug target was available (Bowery and Pratt 1992).

15.4 Norman's pharmacological studies on the GABA_B receptor (1993 – 1997)

Norman went on, with his amazing and contagious curiosity, to inspire collaborators and they tested several compounds such as pertussis toxin in CNS (Knott et al. 1993a; 1993b) or forskolin in spinal cord (Malcangio and Bowery 1993a) and Substance P in rat cortex (Malcangio and Bowery 1993b) and desipramine (Pratt and Bowery 1993) on the recently isolated GABA_B.

Then Norman and Meret Facklam isolated the GABA_B receptor from pigs' brain and found the receptor had the same pharmacological characteristics as those isolated from rats' brain (Facklam and Bowery, 1993). However, these GABA_B receptors were present in homogenates derived from CNS or PNS, and cells membrane, and up to this point there was no evidence of the gene or protein for this pharmacologically characterized receptor. After three more years of further studies combining neurotransmitters, their actions and responses in different compartment of the nervous system, Norman and coworkers make another step forward describing that once GABA_B receptors are activated it can determine opposite effects of up- or down regulation, therefore activation or inhibitions of adenylyl cyclase (Malcangio et al.1995; Knight and Bowery, 1996). Furthermore, Norman with Hill and Hudson start to describe the GABA_B receptors binding site in rat brain (Bowery at al., 1997a).

At the end of 1990s, the application of molecular biology techniques gave a huge burst to the pharmacology field, due to the increasing number of genes cloned for receptors, receptors subunits, and neurotransmitters, and it was the case also for the GABA_B receptor.

Kaupmann et al. (1997) published a paper in Nature reporting the molecular cloning of the gene for GABA_B receptor and the sequence of the protein, including a predicted structure similar to that of the metabotropic glutamate receptors. Norman and David Brown analyzed

the latest scientific development concerning the GABA_B (Bowery 1997; Bowery and Brown 1997).

15.5 When Norman met Alessandra: localization and expression studies of the GABA_B receptor in brain and spinal cord (1998 - 2003)

I met Norman in person at the very end of January 1998, as mentioned in part 15.1. However, at the annual American Society for Neuroscience (SfN) meeting, in New Orleans, LA, in 1997, I already heard scientists referring to Norman as “GABA_B man”, which says all about him. Been called “GABA_B man” meant that he was internationally, worldwide, recognized as the guru, and the father of the GABA_B receptor.

Our collaboration and friendship started that long ago, I cannot believe it is over 25 years ago (scary), but better refocus attention on what we did together concerning the GABA_B receptor research.

In 1998 I began to collaborate with Norman in his laboratory with a fellowship from a European project, at The Medical School in Birmingham, UK. Here we did immunohistochemistry on rat brains to initially localize the GABA_B protein, finding specific patterns of expression in the piriform cortex (Princivalle et al. 2000a). While I was working with Norman, I deepen my knowledge in all what he did scientifically, and how much he had contributed to the knowledge in the field of GABA_B receptor, no wonder why he was referred to as “GABA_B man” (very American way) and what an honor to be there doing research with him!

The European project was based on previous evidence showing a decrease inhibition in the thalamus and somatosensory cortex of non-epileptic rat and Genetics Absence Epilepsy Rats from Strasburg (GAERS), the rat model of *petit mal* or absence seizures. This was a validated model of human absence epilepsy based on neurological, behavioral, and pharmacological findings (Vergnes et al. 1982, Marescaux et al. 1992). So, we started investigating the localization of the GABA_B protein in rat somatosensory cortex and thalamus in adult and developing non GAERS rat brains (Princivalle et al. 2000b). Then we moved forward to investigate the semi-quantitative expression of GABA_B receptor in control rats and GAERS (Princivalle et al. 2003). At the end of 1998 Norman organized a GABA_B Satellite Symposium to the 28th Annual Meeting of the SfN in Los Angeles, CA, of course who else!!! On that occasion Kaupmann and Bettler (1998) unveiled the finer structure of the fully functional GABA_B receptor, demonstrating for the first time that the GABA_B receptor is a metabotropic heterodimeric receptor... no way!!! Norman and I listened to this exciting piece

of news and we both were almost incredulous. This was opening the door to a new and immense field for pharmacological research and treatment of countless diseases. The following year I went back again to Norman's laboratory, and we started a three-year collaboration to finish some of the previous European project to put together the first few papers of our collaboration. Norman offered me a position to work with him on a newer project on GABA_B. I must admit that the idea of working with "**GABA_B man**" was overly exciting and of course how could I say no to such an amazing offer?! So later that year, I started this new position continuing in parallel the previous European project, and other collaborations (Towers et al. 2000; Princivalle et al. 2001) and starting the new project focused on the expression of GABA_B receptor in human sclerotic hippocampi from temporal lobe epilepsy (TLE) affected patients not responding to drug therapies. There was already indirect evidence showing a decreased inhibition in animal model of pharmaco-resistant TLE associated with hippocampal sclerosis (HS). Therefore, our hypothesis was that GABA_B receptor might play a role in this specific category of epileptic patients, and likely to show a lower expression in the hippocampal regions of TLE-HS. From the first part of this project, we used a classical quantitative imaging technique, the autoradiographic binding, using a newly synthesized radioligand with higher affinity for the GABA_B receptor and published these results demonstrating a decreased expression of the GABA_B receptor in the CA3, dentate gyrus, and hilus of the hippocampal region. We found an increased expression of GABA_B receptors per surviving neuron in CA3 of TLE-HS patients compared to post-mortem controls (Princivalle et al.2002). Since with the imaging quantitative technique we investigated the protein receptor and found downregulation of the GABA_B receptor, we wanted to also check if that was due to quantitative differential expression of the transcripts for the GABA_B receptor. We used three different probes to check the three different transcripts for the two splice variants called GABA_{B1} subunit (GABA_{B1a} and GABA_{B1b}) and the second subunit called GABA_{B2} (Kaupmann et al.1998). That research was done using quantitative imaging with *in situ* hybridization technique (Princivalle et al. 2003a). We also investigated the plasticity of GABA_B receptor in heterosynaptic connections at mossy fibers (Chandler et al. 2003).

Norman's 2004-2008

I then moved to a Senior Lecturer position in Sheffield, UK, but that did not mean that our friendship and collaboration were over. In 2004, Norman moved to GSK, Verona, Italy, continuing collaborations with other groups. Norman worked on furtherly expanding knowledge on the GABA_B receptor focusing on physiological aspects and pharmacological properties, within his group (Amantea and Bowery 2004a, Amantea et al.2004b; Smith et al.2007), and in collaboration with others (Dang et al.2004; Meza-Toledo and Bowery 2008).

Norman also wrote reviews about the diverse topics involving GABA_B (Enna and Bowery 2004; Bowery 2006; 2010). His last work before passing away was a chapter in a book edited by the same editor of this book, Giancarlo Colombo, and it was an historical overview of the GABA_B receptor from Norman's initial studies on modelling presynaptic inhibition, passing to the pharmacological characterization, agonist and antagonist, the physiological role, a quick consideration of the distribution in the CNS, the structure, modulation, and clinical aspects targeting the receptor with baclofen as muscle relaxant (Bowery 2016). Part of the work I started in Norman's lab was concluded and published posthumous his death, so much so that the article was dedicated to him (Sheilabi et al. 2017), even if some of the authors never met him but knew about his greatest discovery.

Conclusions

To collaborate with the father of GABA_B receptor and the most inspirational scientist I had met so far, and still, was awesome!!! One other most important quality of Norman was to leave total freedom to the collaborators in technical terms, in cogitating, trying new way for research, in expanding and expressing themselves as researchers and scientists, and the enthusiasm that Norman was capable to spread around to everyone, anywhere, and in any context.

From our collaborations papers were published, but the major lesson by Norman was never give up: if there is a problem we need to find the solutions. Last but not least, taught way of doing research, which I use even now with my own younger collaborators and students, when observing and/or interpreting data was/is: "Do I see what I believe, or do I believe what I see?". This is what every scientist must ask themselves always when they look at their own data. That question represents the essence of an intellectually honest, inspirational, and great scientist like Norman Bowery.

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