Characterization of a GABAergic neurotransmission in adult *Schistosoma mansoni*

D. L. MENDONÇA-SILVA[1], P. F. GARDINO[2], R. C. C. KUBRUSLY[2], F. G. DE MELLO[2] *and* F. NOËL[1]*

[1] *Departamento de Farmacologia Básica e Clínica, Instituto de Ciências Biomédicas,* [2] *Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Cidade Universitária, 21941-590, Rio de Janeiro, Brazil*

(*Received 12 December 2003; revised 26 January and 28 January 2004; accepted 29 January 2004*)

SUMMARY

The neuromuscular systems of parasitic helminths are targets that are particularly amenable for anthelmintics. In this study, we describe a GABAergic neurotransmission in adult *Schistosoma mansoni*, the trematode responsible for high levels of morbidity in people living in developing countries. GABA immunoreactivity (GABA-IR) was detected in nerve cells and fibres of the cerebral ganglia and longitudinal nerve cords and the nerve plexuses ramifying throughout the parenchyma of male adult worms. In addition, strong GABA-IR was also found associated with the oral and ventral suckers as well as in testes indicating a role for GABA in fixation to the host vascular wall and spermatogenesis. The capacity to synthesize GABA from glutamate was confirmed by measurement of a glutamate decarboxylase (GAD) activity. Supporting these data, a single band with an apparent molecular weight of about 67 kDa was detected using an antibody raised against mammalian GAD. *In vivo* studies revealed that picrotoxin, a non-competitive antagonist of the $GABA_A$ receptor, produced a modification of the motility and locomotory behaviour of adult worms, suggesting that GABAergic signalling pathway may play a physiological role in the motonervous system of *S. mansoni* and could be considered as a potential target for the development of new drugs.

Key words: *Schistosoma mansoni*, helminths, GABA, glutamate decarboxylase, nervous system, neurotransmission, immunohistochemistry.

INTRODUCTION

Many authors have suggested that the neuromuscular system of helminths is a target that is particularly amenable for anthelmintics. A better understanding of the neuromuscular physiology of the platyhelminth *Schistosoma mansoni* could thus provide valuable information for the discovery of new drugs active against that particular parasite, responsible for 130 000 deaths per year, and possibly for the other species of this genus. Thus 200 million people infected with schistosomiasis worldwide could be concerned (Fenwick *et al*. 2003). Furthermore, the World Health Organization recently identified schistosomiasis among its top five disease priorities and identified research of new drugs as a major need (Remme *et al*. 2002).

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in vertebrates, has been reported to be present in the nervous system of several invertebrate phyla (Walker & Holden-Dye, 1991). In helminths, such as the nematodes *Ascaris suum* and *Caenorhabditis elegans* (Johnson & Stretton, 1987; McIntire *et al*. 1993), GABA could act as an inhibitory interneuronal and neuromuscular transmitter. Indeed, the ablation of motor neurons containing GABA receptors induced defects in physiological processes such as locomotion and defecation in *C. elegans* (McIntire *et al*. 1993). Moreover, GABA receptors present on somatic muscle cells of *A. suum* mediated an increase in chloride conductance as observed with mammalian $GABA_A$ receptors. However, these *Ascaris* receptors were insensitive to classical mammalian $GABA_A$ antagonists such as bicuculline and picrotoxin, as well as to $GABA_A$ potentiators such as barbiturates, benzodiazepines and neurosteroids (Holden-Dye *et al*. 1989). Such differences between the pharmacological profiles of mammalian and helminthic $GABA_A$ receptors became attractive targets for the development of selective drugs. For instance, the anthelminthic piperazine acts as a GABA agonist at muscular receptors inducing a reversible flaccid paralysis of *Ascaris* (Martin, 1987).

Despite these numerous studies on GABA activities in nematodes, the physiological actions of GABA in platyhelminths has remained relatively poorly explored. This is due, in part, to the small size and inaccessibility of their individual nerve and muscle cells, which make difficult the study of nerve or

* Corresponding author: Departamento de Farmacologia Básica e Clínica, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Cidade Universitária, 21941-590, Rio de Janeiro, Brazil. Tel: +55 (21) 2562 6732. E-mail: fnoel@pharma.ufrj.br

DOI: 10.1017/S0031182004005554 Printed in the United Kingdom