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Review

Gabaergic regulation of the neural organization of fear in the midbrain tectum

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Abstract

In midbrain tectum (MT) structures, such as the dorsal periaqueductal gray (dPAG), the superior colliculus (SC) and the inferior colliculus (IC) GABAergic neurons exert a tonic control on the neural substrates involved in the expression of defensive reactions. In this review, we summarize behavioral, immunohistochemical (brain Fos distribution) and electrophysiological (auditory evoked potentials) data obtained with the reduction of GABA transmission by local injections of a GABA receptor blocker (bicuculline, BIC) or a glutamic acid decarboxylase inhibitor (semicarbazide, SMC) into the MT. Distinct patterns of Fos distribution were obtained following the freezing and escape reactions induced by MT injections of SMC and BIC, respectively. While only the laterodorsal nucleus of the thalamus was labeled after SMC-induced freezing, a widespread increase in Fos expression in the brain occurred after BIC-induced escape. Also, injections of SMC into the IC increased the auditory evoked potentials recorded from this structure. It is suggested that GABAergic mechanisms of MT are also called into play when sensory gating of the MT is activated during different emotional states.

Keywords: Freezing; Escape; Semicarbazide; Bicuculline; GABA; dPAG; Amygdala; SNpr

Contents

1. Introduction

Electrical stimulation of the midbrain tectum (MT)—dorsal periaqueductal gray (dPAG) and deep layers of the superior colliculus (SC)—in the rat elicits unconditioned 'fear-like' behavioral responses, such as alertness, sideways postures, arching of the back, freezing, fleeing locomotion and escape leaps (Bittencourt et al., 2004; Brandão et al., 1982; Graeff et al., 1986; Schenberg et al., 1983). The same pattern of responses has also been observed with electrical stimulation of the inferior colliculus (IC) (Brandão et al., 1988). This defensive behavioral reaction is associated with sensory changes and autonomic responses, such as increase in mean blood pressure, heart rate, piloerection, exhophtalmus, micturition and defecation. In view of these findings, the MT has been suggested to play a major role in the neural

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organization and control of defensive reactions towards threatening stimuli (for reviews see Brandão et al., 1993, 1999, 2003).

The use of electrical stimulation of brain structures in these studies frequently leads to problems in the interpretation of results. Such stimulation frequently activates fibers of passage, raising the possibility of stimulation spreading to neighboring structures. In the case of the IC stimulation, this might include the cuneiform nucleus. To circumvent this problem researchers have also examined the effects of microinjecting tiny volumes (200 nl) of drugs into the MT. The use of this technique in association with electrophysiological studies has provided a large body of evidence for the modulatory influences of an array of neurotransmitters such as GABA, serotonin, neuropeptides, opioids and excitatory amino acids (Bittencourt et al., 2004; Brandão et al., 2003; Graeff et al., 1986). Among them, GABA has been one of the most studied transmitters regarding its regulatory function in the defense reaction integrated at the MT level.

In this paper, we review a series of studies aimed at investigating the role of GABA in sensory gating processes in the MT during different emotional states produced either by electrical or local injections of GABA blockers into the MT, with special emphasis on dPAG and IC. Possible changes in sensory processes have been neglected as a possible source of the defensive behavior reaction that is elicitable via MT stimulation (Brandão et al., 2003; Huston et al., 1990). However, the MT processes aversive sensory inputs and transduces them into behavioral and vegetative nervous system reactions. For example, the IC-induced defensive behavior is accompanied by changes in auditory-evoked potentials in this structure, indicative of a modification of sensory input channels (Brandão et al., 2001). Thus, the behavioral patterns of the defense reaction elicited at the MT level are unlikely to be the result of a localized output process. As in the case of hypothalamic aggression (Bandler, 1982a,b; Bandler and Flynn, 1971, 1972; Flynn et al., 1971; MacDonne and Flynn, 1966) and the central activation of the perioral biting reflex, they are probably linked to changes in sensorimotor gating processes (Huston et al., 1980; Welzl et al., 1984).

While it is well established that there are four columns in the central gray, as identified anatomically, their functional role is still a subject of great debate (Bandler and Carrive, 1988; Bandler and Shipley, 1994; Carrive, 1993). It seems very likely, however, that different pools of neurons in the midbrain central gray are responsible for the elaboration of distinct aspects of the defensive behavior. Dorsolateral and dorsomedial columns have been associated with freezing, escape, hypertension, tachycardia, and serotonin-dependent analgesia, the lateral column with attack and the ventrolateral column with quiescence, fear conditioned freezing, recuperative-like behaviors, hypotension, bradycardia and opioid-dependent analgesia (Brandão et al., 2003; Bittencourt et al., 2004; Canteras and Goto, 1999; De Oca et al., 1998; Walker and Carrive, 2003; Vianna and Brandão, 2003).

2. Tonic inhibition of the neural substrates of defensive behavior by GABAergic neurons

GABA exists in appreciable density in the MT, and GABAergic inhibition controls the firing rate of neurons in this region (LeBeau et al., 1996, 2001; Roberts and Ribak, 1987; Thompson et al., 1985). As aversive states are produced by GABA-$_A$ blockers and inhibited by GABA-$_A$ agonists locally injected into the dPAG and the IC, it has been suggested that these structures contain a tonically active GABAergic network that regulates these states through GABA-$_A$ receptors (Audi and Graeff, 1984; Behbehani et al., 1990; Brandão et al., 1982, 1986, 1988, 1999; Coimbra and Brandão, 1993; DiScala et al., 1983; Sandner et al., 1981; Schenberg et al., 1983). Consistent behavioral evidence has also been provided for an anti-aversive action of benzodiazepines in the MT. Indeed, local injections of benzodiazepines into the MT depress the defensive behavior induced by stimulation of this region (Audi and Graeff, 1984; Brandão et al., 1982; Melo et al., 1992; Pandóssio and Brandão, 1999).

In this review, we will concentrate on the distinct sensorimotor effects following the injections of bicuculline (BIC) and semicarbazide (SMC) into the MT. BIC is a post-synaptic GABA receptor antagonist, while SMC causes a reduction in GABA levels due to its inhibition of glutamic acid decarboxylase (GAD), the enzyme responsible for the GABA synthesis (Brandão et al., 1986; Killam and Bain, 1957). Injections of SMC or BIC into the MT produce defensive behavior, which mimics the effects of its electrical stimulation (Brandão et al., 1982, 1986, 1988; DiScala and Sandner, 1989). However, while BIC causes a full-blown behavioral activation with escape responses predominating, the defensive reaction caused by SMC has a slow onset and freezing behavior predominates. Freezing and escape are negatively correlated, suggesting a competition between these fear-related motor systems. The distinct defensive responses induced by these drugs could be due to different degrees of GABA inhibition, as BIC (being a receptor antagonist) would cause an immediate GABA inhibition whereas the SMC, by reducing its synthesis, would cause less intense antagonism.

These same defensive responses may also be produced by drugs acting at glutamate receptors, as recently reported in a Fos study from this laboratory. Glutamate injected into the dPAG caused a selective activation of the laterodorsal nucleus of the thalamus and other structures involved in the sensory processing of aversive information, such as the superior and inferior colliculi. NMDA, similarly injected, produced a distribution of Fos in the brain that was quite different from glutamate. NMDA caused widespread activation throughout the forebrain but only in structures