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Experimental Neurology 191 (2005) 225–242

Experimental Neurology

www.elsevier.com/locate/yexnr

Intrinsic neural circuits between dorsal midbrain neurons that control fear-induced responses and seizure activity and nuclei of the pain inhibitory system elaborating postictal antinociceptive processes: a functional neuroanatomical and neuropharmacological study

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Received 10 February 2004; revised 1 October 2004; accepted 5 October 2004
Available online 19 December 2004

Abstract

The blockade of GABA-mediated Cl^- influx with pentylenetetrazol (PTZ) was used in the present work to induce seizures in *Rattus norvegicus*. The aim of this work was to study the involvement of monoamines in the antinociception induced by convulsions elicited by peripheral administration of PTZ (64 mg/kg). The analgesia was measured by the tail-flick test in seven or eight Wistar rats per group. Convulsions were followed by statistically significant increase in the tail-flick latencies (TFL), at least for 120 min of the postictal period. Peripheral administration of methysergide (0.5, 1, 2, and 3 mg/kg) caused a significant decrease in the TFL in seizing animals, as compared to controls, in all postictal periods studied. These findings were corroborated by the pretreatment with ketanserin, a 5-$HT_{2A/2C}$-serotonergic/α_1-noradrenergic receptors antagonist, at the same doses. Peripheral administration of yohimbine (0.5, 1, 2, and 3 mg/kg), α_2-noradrenergic antagonist, also decreased the postictal analgesia either at initial or more terminal periods of the postictal analgesia. These data were corroborated with peripheral administrations of propranolol, a β-noradrenergic receptor blocker that caused a decrease in the postictal analgesia consistently in later stages (after the first 20-min post-tonic-clonic convulsive reactions) of the postseizure analgesia, except for the highest dose. These results indicate that monoamines may be involved in the postictal analgesia. The blockade of 5-$HT_{2A/2C}$-serotoninergic, α_1-noradrenergic, or α_2-noradrenergic receptors before tonic clonic seizure-induced analgesia antagonized the increase in the nociceptive threshold caused by seizures in initial steps of the temporal antinociceptive curve, as compared to the blockade of β-noradrenergic ones. These findings suggest that the recruitment of α-noradrenergic receptor and serotonergic receptors was made immediately after convulsions and in other initial periods of the postictal analgesia, as compared to the involvement of β-noradrenergic receptor. Neurochemical lesions of the locus coeruleus (LC) and neuronal damage of the dorsal raphe nucleus induced a significant decrease of the postictal analgesia, suggesting the involvement of these nuclei in this antinociceptive process. The functional neuroanatomical study of the neural link between the mesencephalic tectum and nuclei of the central pain inhibitory system showed evidence for the interconnection between superior colliculus, both dorsal and ventral periaqueductal gray matter (PAG), and inferior colliculus. Defensive substrates of the inferior colliculus, also involved with wild running and epilepsy, send inputs toward dorsal raphe nucleus and locus coeruleus. Since these nuclei are rich in monoamines and send neural connections toward other monoaminergic nuclei of the brainstem involved with the control of the nociceptive inputs in the

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0014-4886/$ - see front matter
doi:10.1016/j.expneurol.2004.10.009

dorsal horn of the spinal cord, the present results offer a neuroanatomical and psychopharmacological basis for the antinociceptive processes following tonic-clonic seizures.

Keywords: Postictal analgesia; Pentylenetetrazol; GABA-A receptor; Serotonin; Noradrenaline; 5-HT_{2A} serotonergic receptor; α_1-, α_2-, and β-noradrenergic receptors; Epilepsy; Pain

Introduction

The neuroantomical basis of the analgesia (Basbaum and Fields, 1984, 1989) and the neural substrates involved in the generation and propagation of the epileptogenic activity in the central nervous system (Basbaum and Fields, 1989; Ribak et al., 1997; Tsutsui et al., 1992) are focus of many investigations in the field of neuroscience and experimental neurology. Previous studies indicate a correlation between temporal lobe epilepsy in adult patients and the occurrence of seizure and status epilepticus (Margerison and Corsellis, 1966; Sagar and Oxbury, 1987). Nociception threshold seems to be spontaneously high in patients with temporal lobe epilepsy (Basbaum and Fields, 1989). Rodents which have congenital audiogenic seizures and high responses to peripheral electric stimulation-induced analgesia present low brain cholecystokinin, an anticonvulsant and antiopioid neuropeptide, which increase behavioral abnormalities of rats with audiogenic seizures (Zhang et al., 1997b). Recent findings in the literature demonstrated antinociceptive processes in experimental models of epilepsy, in which μ_1-opioid, 5-HT_2, and both muscarinic and nicotinic cholinergic receptors may be involved (Coimbra et al., 1996, 2001a; Freitas et al., 2004). In fact, some structures and neural brainstem networks, such as the inferior colliculus, the dorsal periaqueductal gray matter (PAG), the dorsal raphe nucleus, the nucleus reticularis gigantocelularis, pars alpha, and the locus coeruleus (LC) have endogenous opioid-, monoamine-, and acetylcholine-mediated mechanisms involved in the control of pain (Azami et al., 2001; Basbaum and Fields, 1984; Rosa et al., 1998), defense (Coimbra et al., 2000; Eichenberger et al., 2002; Monassi et al., 1997; Osaki et al., 2003), and epilepsy (Cardoso et al., 1994; Garcia-Cairasco et al., 1993a,b; Peterson et al., 2000). Many of these nuclei are interconnected and send projections to the dorsal horn of the spinal cord, controlling the synapses between the first and the second neurons of the spinal-thalamic nociceptive pathways (Azami et al., 2001; Basbaum and Fields, 1989; Li et al., 1993; Rosa et al., 1998). Monoaminergic systems of the locus coeruleus and dorsal raphe nucleus are particularly involved in the control of pain, seizures, and epilepsy generated in prosencephalic structures (Shouse et al., 2001; Wang and Nakai, 1994; Zhang et al., 1997a). Although the descending control by dorsal periaqueductal gray matter and dorsal raphe nuclei on nociceptors in the trigeminal sensory nuclei and the dorsal horn of the spinal cord is mainly mediated by serotonin-containing neurons in the raphe magnus nucleus, there are also direct projections from serotoninergic neurons of the continuum dorsal periaqueductal gray/dorsal raphe nucleus to the trigeminal sensory complex and spinal cord (Beitz, 1982; Bowker et al., 1981; Li et al., 1993).

The pentylenetetrazol (PTZ) is a GABAergic noncompetitive antagonist that does not interact directly with GABA receptors, but blocks the GABA-mediated Cl^- influx. The intraperitoneal (IP) injection of PTZ in rats causes tonic-clonic seizures (Coimbra et al., 2001a,b; De Lima and Rae, 1991). The study of GABAergic and monoaminergic mechanisms can offer elucidative data about the neurochemistry of the postictal analgesia and also about the neural pathways that can be used for the control of hyperactivity of the neurons located in the dorsal midbrain (Coimbra and Brandão, 1993; Eichenberger et al., 2002). In fact, serotonin and noradrenaline seem to be critically implicated in the control of brain epileptogenic activity (Bengzon et al., 1999; Statnick et al., 1996a,b) and also in the control of the capacity of perception of pain (Castilho et al., 1999; Coimbra and Brandão, 1997; Coimbra et al., 1992) through neurochemical processes induced by stimulation of structures where it is also possible to induce convulsive reactions (Cardoso et al., 1994; Garcia-Cairasco and Sabbatini, 1991; Ribak et al., 1997; Terra and Garcia-Cairasco, 1994). Considering the inferior colliculus, an important structure for processing acoustic signals, there is a great deal of anatomical evidence of connective pathways between the central nucleus and the external cortex, the major anatomical aspects of the inferior colliculus involved in acoustic coding and maybe epilepsy (Chakravarty and Faingold, 1997; Coleman and Clerici, 1987). However, the neurophysiology and fine intracollicular neural networks and also the possible interactions between the inferior colliculus and other nuclei of the brainstem involved with antinociceptive processes are not well understood.

In this work, we demonstrate the effect of the nonspecific blockade of serotonergic receptors (using methysergide), the effect of 5-$HT_{2A/2C}$-serotonergic/α_1-noradrenergic receptor blockade (with ketanserin), and the effect of peripheral pretreatment with either specific α_2-noradrenergic (yohimbine) or nonspecific β-noradrenergic (propranolol) pharmacological antagonists on the postictal analgesia induced by seizures elicited by a systemic blockade of Cl^- channels linked to GABAergic synapses in the central nervous system. The relevance of some nuclei rich in serotonin and norepinephrine, such as the dorsal raphe nucleus and the