ANTICONVULSANT EFFECTS OF ORPHANIN FQ ON SEIZURES INDUCED BY PENTYLENETETRAZOLE

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It has been suggested that opioid-like OP4 receptor and its endogenous agonist named orphanin FQ, modulate a variety of physiological processes. The wide distribution of OP_4 receptor and orphanin FQ and their ability to modulate neurotransmitter release suggest that orphanin may be involved in the pathogenesis of convulsions. Previous studies indicated that orphanin exerts proconvulsant as well as anti-convulsant activity (1-2). In the present study we evaluated whether intracerebroventricular (i.c.v.) administration of orphanin affected behavioural convulsions induced by (the stimulant blocking GABA-A receptors) pentylenetetrazole, or (the glycine receptor antagonist) strychnine, in CD1 mice. Orphanin (Tocris, UK), pentylenetetrazole and strychnine (Sigma Aldrich, Italy) were dissolved in sterile normal saline (vehicle). Orphanin (OFQ, 2-5 nmol /2 µl i.c.v.) or the same volume of vehicle (2 µl i.c.v.) was administered, 30 min before pentylenetetrazole (PTZ, 75 mg/kg intraperitoneally, i.p.) or strychnine (1.3 mg/kg, i.p.). The animals were observed for 30 min after the injection of the convulsant, for clonic and tonic convulsions as well as for lethality. A few minutes after administration of pentylentetrazole, behavioural changes such as myoclonic jerk, generalized clonic seizures and tonic extension could be observed. Tonic generalized extension also occurred after strychnine injection. Almost all animals showing tonic generalized extension died. Pre-treatment with orphanin did not prevent seizures and mortality induced by strychnine. On the contrary, orphanin delayed the appearance of seizures, reduced the number of tonic-clonic convulsions and the death of animals induced by pentylenetetrazole (deaths: vehicle + PTZ 9/10; OFQ 2 nmol + PTZ 2/10*; OFQ 5 nmol + PTZ 1/10*; * is for $P<0.01$ vs vehicle + PTZ treated animals - Fisher's Exact test). It is well known that epilepsy may depend on a disruption of balance between excitatory (mainly glutamatergic) and inhibitory (GABAergic) neurotransmission. Since orphanin inhibits glutamate release in rat cortical slices (3), we can speculate that the inhibitory effect of the peptide on glutamatergic transmission might contribute to its anticonvulsant action.

1) Bregola G., Zucchini S., Frigati L., Candeletti S., Romualdi P., Reinscheid R., Simonato M. (2002) Epilepsia 43: 18-19. 2) Gutierrez R., Leff P., Romo-Parra H., Acevedo R., Anton B. (2001) Neuroscience 105: 325-333. 3) Nicol B., Lambert D.G., Rowbotham D.J., Smart D., McKnight A.T. (1996) Br. J. Parmacol. 119 :1081-1083.