Title : CLONIDINE ABATES CENTRAL NORADRENERGIC HYPERACTIVITY INDUCED BY IMMOBILIZATION STRESS.

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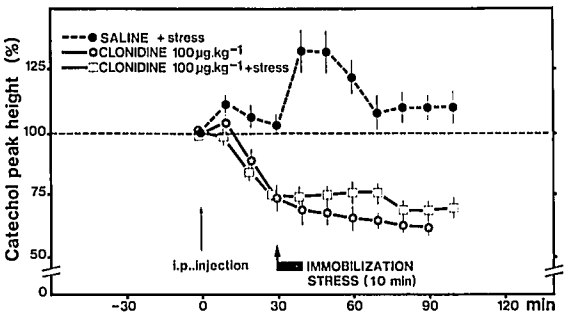
Introduction : Narcotic anesthesia has gained popularity, during the last decade, in major surgery, due to a lack of myocardial depression, and cardiovascular stability under surgical stimuli. Further studies have questionned such a stability or pointed out the risk of prolonged or recurrent respiratory depression and called for the search of other central agents able to a) potentiate narcotic induced analgesia and control hyperdynamic cardiovascular reactions during the whole perioperative period and b) induce minimal myocardial and respiratory depression, and delayed awakening. Central noradrenergic (NA) system has been implicated both in the central control of blood pressure and in the response to stress. Alpha 2 agonists, such as clonidine, have been shown to decrease the activity of this NA system (1) and control a) hypertension without myocardial depression (2), b) narcotic/ethanol withdrawal symptoms. The possibility to reliably monitor central NA activity using in vivo electrochemical detection, under strictly chronic conditions (3), has permitted the investigation, in freely moving rats, of the effect of clonidine on central NA hyperactivity. The latter was induced by immobilization stress, and assessed by 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the extracellular space of the locus coeruleus (LC) which is the largest cluster of NA neurons in the brain stem.

Methods : Naive rats (280g, OFA strain, Iffa Credo, 69 Les Oncins, France) were implanted with guiding cannula in the LC and appropriate electrical wires, 48h before the experiments, which were conducted between 10 AM and 4 PM. On the day of the experiment, a treated carbon fiber microelectrode was threaded through the cannula and connected via appropriate cables to allow DOPAC monitoring in the LC (3). After at least 50 min of stabilization of the catechol peak, corresponding to DOPAC oxydation, freely moving rats were treated with various amounts of clonidine (50,100,200 mcg.kg^{-1} i.p.) or saline (0.5 ml i.p.) 30 min before immobilization stress (10 min ; the rat was held in the hand of the experimentator, without any interference with ventilation or nociceptive stimuli). Recording of the catechol peak was done every 2 min during the experiment. Control value (100%) was taken as the mean of 5 catechol peaks heights recorded during the last 10 min before i.p. injection. Results are expressed as variations of catechol peak heights (%) as compared to the control value (100%). The variations are reported in the figure according to the different treatments : clonidine 100 mcg.kg^{-1} i.p. followed 30 min after by stress, as compared to saline followed by stress or clonidine 100 mcg.kg^{-1} without stress.

Results : Clonidine 100 mcg.kg^{-1} i.p. given 30 min before stress (n=5) diminished by 25% ± 3 (mean ± sem) the catechol peak height and then totally abated the increase induced by stress. On the contrary, clonidine 50 mcg.kg^{-1} did not blocked this increase. No statistically significant difference (Dunnett test) was found between the results obtained with clonidine 100 mcg.kg^{-1} alone or clonidine 100 mcg.kg^{-1} followed by immobilization stress. Saline treated rats (n=6) exhibited a 32% ± 5 increase in the catechol peak 12 min after the beginning of stress.



Discussion : These results indicate an original way to suppress, with minimal sedation, the central NA-LC neurons hyperactivity induced by stress. Moreover, this is the first attempt to evaluate under strictly chronic conditions the pharmacological modulation of central NA activity. The dose of clonidine sufficient to abate the stress response seems to be specific of alpha 2 receptors according to biochemical and electrophysiological (1) data. The blockade of NA hyperactivity does not seem to be a consequence of a major decrease in the cerebral perfusion pressure since the magnitude of hypotension induced by clonidine 50 mcg.kg^{-1} is, according to the litterature, approximately the same as the hypotension induced by clonidine 100 mcg.kg^{-1}. These results are in agreement with reports showing analgesic properties of alpha 2 agonists and their abilities to control sympathetic hyperactivity induced by narcotic withdrawal. These results may open a new way to supplement balanced/narcotic anesthesia. They may also suggest a new way to induce controlled hypotension without rebound symptoms or to control hyperdynamic cardiovascular reactions. They call for a controlled clinical trial of alpha 2 agonists to see if such drugs may improve cardiovascular stability and/or decrease narcotic or sedative requirements, without untoward effects, in the ICU or anesthetic settings.

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