ABSTRACT

The Effect of Some Nitric Oxide Donors on the Central Nervous System and Related Functions in a Normal Rat Model

Kesi Jamila Brown

Nitric oxide is a small molecule with big biological roles with functions in diabetes, inflammation, and learning leading to an increase in the number of donors being synthesized since these roles were first identified. This research sought to determine the effect of a fairly new nitric oxide donor, S-nitroso-L-cysteine ethyl ester hydrochloride (SNCEE.HCl), on learning and memory, carbohydrate metabolism and haemodynamic parameters and compare with other more commonly used donors, S-nitrosoglutathione (GSNO), S-nitrosocaptopril (CapSNO) and S-nitroso-N-acetyl-D,L-penicillamine (SNAP). This was done through the use of the Morris Water Maze, the Oral Glucose Tolerance Test, the CODA6 non-invasive pressure recording system in addition to an in vitro method of determining the conversion of short-term potentiation (STP) to the cellular correlate of learning, long-term potentiation (LTP), in hippocampal slices.

Results of the water maze experiment indicated no improvement in the time it took the animals to learn the task, i.e. solve the maze. Intravenous administration of 10 mg/kg BW SNCEE.HCl (10.0 ± 1.08 seconds) but not GSNO (5.0 ± 0.41 seconds) and SNAP (1.75 ± 1.44 seconds), was able to significantly improve memory recall (as tested by the length of time spent in the quadrant of the pool where the platform was previously located) compared with the control (4.2 ± 0.66 seconds). The same was also true when a higher dosage of 30 mg/kg BW was used, where SNCEE.HCl (9.75 ± 1.50 seconds) showed a significant increase in the time spent in the platform quadrant which was not observed in the GSNO-treated group(5.25 ± 0.75 seconds; p < 0.05 where significant). Co-administration of the nitric oxide synthase inhibitor, L-NAME, showed some impairment in the speed at which the animals learnt the task toward the end of the experiment (trials 8 and 12) in all groups but was not consistent. Probe test analysis indicated no significant difference in the RSNO + L-NAME treated groups when compared with the control.

Further analysis into the ability of the donors to convert STP to LTP in hippocampal slices indicated that at a concentration of 0.1 mM, no donor was able to convert STP to LTP. At a higher concentration of SNCEE.HCl (10 mM) there was a depression of the potentials which recovered only after the donor was washed out of the system with a significant increase in the potentials through to the end of the experiment.
In contrast to other donors, SNAP and CapSNO, haemodynamic assessment indicated that SNCEE.HCl was a poor hypotensive agent. In addition, it did not show the hyperglycaemic effect either prior to or following a glucose challenge as was seen with both SNAP and GSNO. These results were accompanied by increases in plasma nitrite levels when dosages of 10 mg/kg BW of the donors were administered 30 minutes prior to blood collection with SNAP (75.50 ± 4.55 μM) showing the greatest increase and SNCEE.HCl the least (31.76 ± 1.85 μM) versus the control (23.33 ± 1.38 μM). Histological assessment of the major organs, liver, kidney, brain and lungs, showed no significant damage to the organs and no significant changes between the RSNO-treated and control groups.

The data therefore indicated that SNCEE.HCl was capable of improving spatial memory retention but not formation with no adverse effect of blood pressure and carbohydrate metabolism through its production of nitric oxide in vivo which was not observed with other RSNOs. These results suggest a possible role for this donor in disease states where memory deficits prevail such as Alzheimer’s disease.

Keywords: Kesi Jamila Brown; nitric oxide donors; central nervous system; spatial memory; long-term potentiation; glucose metabolism; haemodynamic parameters.