Enhancement of dopamine release induced by new class of nitric oxide donor derived from piloty acid: an *in vitro* microdialysis study

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Parkinson disease (PD) is a degenerative brain disorder characterized by motor symptoms that are associated with the loss of dopaminergic (DA) neurons in the substantia nigra (SN). Nitric oxide (NO) belongs to a new class of gaseous signaling molecules with fundamental functions in biology (Serra et al., 2003; Aquilano et al., 2008). Numerous studies *in vitro* and *in vivo* showed that NO-generating drugs (NO donors) cause an increase of the extra-cellular level of dopamine in the striatum (Serra et al., 2001). This could suggest a possible application of such NO-donors in the study of dopamine modulation in Parkinson's disease. In this study, we evaluated the effects on the dopamine release by PC12 cell line by a new class of Nitric Oxide donor.

PC12 represents a valuable model for many features of central dopaminergic neurons. We investigated the effects of a new class of NO donors derived from piloty's acid (PI), widely known as NO donor (Shirota et al., 1999). Different derivatives were synthesized by adding electron-withdrawing or electron-donor groups in order to modulate NO release from those compounds. We evaluated the effects of N-hydroxy-4-nitrobenzenesulfonamid (4-NO_2-PI) and N-hydroxy-4-methoxybenzenesulfonamide (4-OMe-PI) on the dopamine release from PC12 cell suspensions by means of capillary microdialysis (Serra et al., 2003). S-nitroso-*N*-acetilpenicillamine (SNAP) is widely known as NO donor, so this was used as reference compound. NO released from NO donors was amperometrically detected by means of epoxycarbon - based microsensors, by applying a constant potential of + 865 mV vs Ag/AgCl. DA was measured by means of HPLC equipment coupled with an electromedical detector. All NO-donors were infused at 1.0 mM concentration for 60 min. SNAP infusion induced a progressive and significant increase in DA concentration. In the same conditions, both PI and 4-MeO-PI infusion induced a statistically significant increase in DA levels. Conversely, the infusion of 4-NO_2-PI determined a significant decrease in DA concentration.

The experimental data show that Piloty's Acid derivatives both are able to release NO but with different mechanisms. In fact the presence of 4-NO_2-PI determined a fast release of NO, producing a decrease on DA concentration. On the contrary, the presence of the 4-MeO-PI resulted in a slower NO release, determining an increased DA concentrations. Those findings could suggest a potential use of PI derivatives whit electron-withdrawing or electron-donor groups as dopamine release modulators in PD.

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