Behavioral Evaluation of An Accelerated Stroke Models Induced by Chronic Inhibition of Nitric Oxide Synthase.

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The L-arginine-nitric oxide (NO) system is thought to play an important role in the regulation of platelet function1) as well as cardiovascular function2-4). It has been reported that chronic inhibition of NO synthesis produced an increase in blood pressure (BP) and accelerated the onset of stroke in stroke-prone spontaneously hypertensive rats (SHRSP)5). The purpose of the present study was to develop a rat model for cerebro-vascular dementia by chronic infusion of a NO synthase inhibitor to stroke-prone spontaneously hypertensive rats (SHRSP) and evaluate it behaviorally. The effects of ibudilast which is an activating drug of cerebral circulation on behavioral changes was also elucidated.

**Methods:** Rats were subjected to a 12 hour dark and light alternation cycle. Ambulatory and drinking activities were determined simultaneously and were subjected power spectral analysis. N^•^-nitro-L-arginine methylester (L-NAME), a NO synthase inhibitor, was administered for 4 weeks via osmotic minipumps delivering 60 μl/day of 0.02 M solution which were implanted intra-peritoneally into 16 week-old male SHRSP. Ibudilast was mixed into regular rat chow as estimated dose of 1 mg/kg/day and administered to 10 week-old SHRSP. In another series of experiment, platelet aggregability in response to collagen and ADP were measured in platelet-rich plasma from ibudilast/L-NAME-treated SHRSP and were compared with those from L-NAME-treated and untreated SHRSP.

**Results:** After the 4-week L-NAME treatment, 84% (n=19) of SHRSP died from stroke. Both collagen (1-50 μg/ml) and ADP (1-10 μM) produced platelet aggregation in a concentration-dependent manner. L-NAME treatment augmented platelet aggregability in SHRSP. Ibudilast depressed the changes in platelet aggregability, the dose-response relationships in collagen and ADP-induced platelet aggregation in ibudilast/L-NAME-treated SHRSP were almost comparable to those in untreated SHRSP. Abrupt increase and desynchronization with light and dark alternation cycle of both ambulatory and drinking activities were observed in L-NAME-treated SHRSP died from stroke. In addition to circadian rhythm, longer periodicity was noted as reported in untreated SHRSP after the onset of stroke6). Ibudilast decreased the frequency of SHRSP showing rhythmic abnormalities in both ambulation and drinking.

**Conclusion:** Chronic inhibition of NO synthase accelerated the onset of stroke and resulted in a high mortality in SHRSP, accompanied with behavioral changes. The findings that ibudilast ameliorated the changes in platelet aggregability and behavior suggest that the mechanisms underlying accelerated stroke by chronic inhibition of the NO synthesis in SHRSP might involve an increase in platelet aggregability.

**References**