7-Nitroindazole enhances dose-dependently the anticonvulsant activities of conventional antiepileptic drugs in the mouse maximal electroshock-induced seizure model

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Abstract:
7-Nitroindazole (7NI, a nitric oxide synthase [NOS] inhibitor) administered intraperitoneally (ip), 30 min before the test, at doses ranging between 50–200 mg/kg, raised the threshold for electroconvulsions in mice. Linear regression analysis revealed that the doses increasing the threshold by 50% (TID₁₀) and 100% (TID₂₀) over the control value for 7NI were 115.2 and 173.4 mg/kg, respectively. Moreover, 7NI dose-dependently potentiated the anticonvulsant effects of four conventional antiepileptic drugs (AEDs: carbamazepine – CBZ, phenobarbital – PB, phenytoin – PHT, and valproate – VPA) in the mouse maximal electroshock-induced seizure (MES) model. 7NI at 50 mg/kg enhanced only the anticonvulsant effect of PB, whereas the drug at 75 and 100 mg/kg potentiated the antiseizure effects of PB, PHT and VPA, but not those of CBZ against MES-induced seizures. Only 7NI at 150 mg/kg enhanced considerably the antielectroshock action of all studied AEDs in the MES test. Pharmacokinetic evaluation of interactions between 7NI and the investigated AEDs revealed that 7NI (150 mg/kg; ip) did not alter total brain concentrations of conventional AEDs in mice. L-arginine (L-Arg – a natural precursor of NO; administered ip), 500 mg/kg, 60 min before electroconvulsions) did not reverse the activity of 7NI (150 mg/kg), but in contrast, it significantly potentiated the anticonvulsant action of conventional AEDs combined with 7NI (150 mg/kg). Pharmacokinetic increase in total brain AED concentrations was observed for the combinations of L-Arg (500 mg/kg) with 7NI (150 mg/kg) and PHT (by 32%; p < 0.01) or VPA (by 22%; p < 0.05). Neither total brain CBZ nor PB concentrations were altered following the co-administration of L-Arg (500 mg/kg) with 7NI (150 mg/kg). 7NI at doses of 100–200 mg/kg significantly impaired spontaneous ambulatory activity in mice subjected to the Y-maze task. The NOS inhibitor at doses of 50 and 75 mg/kg had no significant effect on locomotor activity of animals, although the number of arm entries within the 5 min of observational time was reduced. Finally, it can be concluded that the enhancement of anticonvulsive efficacy of CBZ, PB, PHT and VPA by 7NI alone or in combination with L-Arg in the MES test, deserves more attention and further neurochemical studies are required to elucidate the exact role of NO in the brain.

Key words:
7-Nitroindazole, L-arginine, nitric oxide, maximal electroshock, electroconvulsive threshold, carbamazepine, phenobarbital, phenytoin, valproate, pharmacodynamic/pharmacokinetic interactions, spontaneous locomotor activity