

Effects of amphetamine and caffeine on jumping behavior and brain NADH in rats

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ABSTRACT The effects of amphetamine (1.5 mg/kg ip) and caffeine (120 mg/kg ip) on jumping behavior induced by footshock in rats and on the concentrations of the reduced nicotinamide adenine dinucleotide (NADH) of brain were studied in 40 rats from the point of view about the regional brain metabolism. Amphetamine potentiated strongly the induced jumping behavior, while it increased NADH concentrations in hippocampus, cerebellum, frontal cortex, caudate nucleus and diencephalon. Caffeine increased NADH concentrations in the studied six brain structures while it potentiated the jumps in the first 3 min, but the effects of caffeine were quickly reversed. Caffeine decreased NADH concentrations in 6 brain structures and rat's jumps in the 5th min.

KEY WORDS amphetamine, caffeine, jumping behavior, NAD, hippocampus, cerebellum, caudate nucleus, diencephalon, frontal cortex

The positron emission tomography has already revealed the new facts about the relationship between the psychological processes and the regional brain metabolism of glucose⁽¹⁻³⁾. Although there are a lot of references about pharmacological mechanism of amphetamine in respect to the central transmitters. We are trying to investigate the behavioral pharmacology of amphetamine and caffeine from the point of view about the regional brain metabolism of glucose. we have found that the increased NADH in brain from both extra and intra sources are related to the enhanced jumps in the rats⁽⁴⁾. Amphetamine with *l*-dopa increased the jumping behavior of mice⁽⁵⁾.

Caffeine increased mouse activity⁽⁶⁾. In the experiment, we are going to compare the differences between effects of amphetamine and caffeine on the induced jumps of rats. Furthermore, we are going to inquire into the relationship between the regional brain NADH acted by the drugs and the jumping behavior.

METHODS

40 rats weighing $275 \pm \text{SD } 25$ g were divided randomly into 4 groups of 10. Saline, amphetamine (*d*-amphetamine sulfate, Sigma London), caffeine (Tianjin Med Corp) were administered to the rats 0.5 ml, ip, 1.5 mg/kg, and 120 mg/kg respectively. According to other finding^(6,7), caffeine 150 mg/kg, amphetamine 1.5 mg/kg in the rats elicited the maximum locomotor responses in photocell. In this experiment, we found that caffeine 120 mg/kg was the optimum dose for the maximum jumping behavior.

The experimental apparatus was the same as it was used in our last experiment⁽⁴⁾. The rats in the first three groups were put in the tube for 5 min after 15 min following administration of the drug, the rats received 65 electroshock on the foot for 5 min. The rats in the last group received 39 electroshocks on the foot for 3 min after 15 min following the injection of caffeine. The electroshock was a series of rectangular waves of 50 Hz from an electronic stimulator. The intensity of electroshock was 25 V lasting 0.2 s. The different height of jumps induced by footshock in the tube were recorded by photoelectrical technique. The rat was quickly decapitated and

the brain was dissected after the behavior procedure. Frontal cortex, caudate nucleus, hippocampus, diencephalon structure, cerebellum and brain stem were separated according to rat brain atlas⁽⁸⁾. The NADH concentrations of each brain structure were biochemically analyzed according to the method previously described⁽⁴⁾.

RESULTS

The results in the behavioral procedure were shown in Fig 1. The number of jumps of the rats injected amphetamine were greater than those of the rats injected saline. The differences between saline group and amphetamine group were significant for all 4 heights in the experimental tubes ($p < 0.001$). The number of jumps in the rats injected caffeine were just a little bit larger than those of the saline group in all 4 heights but only the difference in the lowest height between the caffeine group and the saline group was significant ($p < 0.05$).

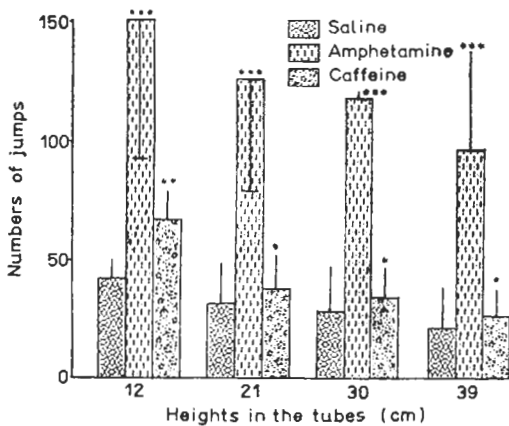


Fig 1. Effects of amphetamine and caffeine on the numbers of induced jumps. 10 rats/group, $\bar{x} \pm SD$. * $p > 0.05$, ** $p < 0.05$, *** $p < 0.01$ compared to saline group.

When we analyzed the dynamic process of the induced jumps during the experimental period of 5 min, we found that the behavior response curves of amphetamine of all 4 heights in the tube were alike in

appearance. The numbers of rat's jump at the 3rd min were the highest.

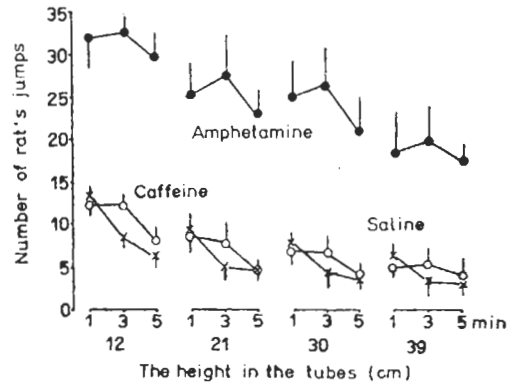


Fig 2. Response curves of the induced jump. 10 rats/group. The differences in all points between amphetamine and saline are significant ($p < 0.01$); the points between the curves of caffeine and saline are not significant, except the point at the 3rd min of the lowest height ($p < 0.05$).

Contrary to amphetamine group, the saline group had the different response curves. The largest numbers of rat's jump at all 4 heights took place in the 1st min, then decreased minute by minute. All the number of jumps in amphetamine response curves were significantly larger than the correspondences in the saline behavior curves. The number of jumps at the 3rd min of the caffeine group at all 4 heights in the tube were slightly larger than those of the saline group. Only the difference at the 3rd min of the lowest height between caffeine group and saline group was significant ($p < 0.05$).

The results of biochemical analysis of the discrete brain structures showed as Fig 3.

Amphetamine (1.5 mg/kg ip) increased the NADH concentrations in frontal cortex, caudate nucleus, hippocampus, diencephalon and cerebellum. All of the differences in NADH concentrations of the mentioned correspondent brain structures

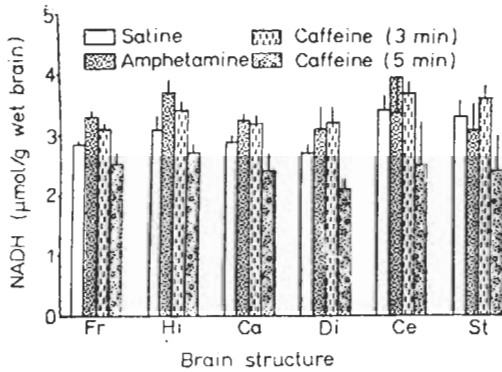


Fig 3. Concentrations of NADH in 6 brain structures. 10 rats/group. Fr=frontal cortex; Ca=caudate nucleus; Hi=hippocampus; Di=diencephalon; Ce=cerebellum; St=brain stem. The differences in NADH concentrations between two caffeine groups and saline group are significant ($p < 0.01$); the differences between amphetamine group and saline group are significant ($p < 0.01$), except the difference in brain stem ($p > 0.05$).

between amphetamine group and saline group were significant ($p < 0.01$). But the difference in NADH concentration of brain stem between amphetamine group and saline group was not significant. Contrary to amphetamine, caffeine (120 mg/kg ip) decreased the concentrations of NADH in all 6 brain structures of the rats which were decapitated at the 5th min electroshock, but the NADH concentrations in discrete brain structures of the rats who were killed at the 3rd min increased as much as those in the rats injected amphetamine and the differences in all of the corresponding brain structures between caffeine group and saline group reached significant levels ($p < 0.01$).

DISCUSSION

The brain NAD/NADH ratio decreased slightly during alcohol treatment in the mice⁽⁹⁾. Low ethanol doses were accompanied by increasing level of NADH in rats and cats⁽¹⁰⁾. The distribution of *d*-amphetamine in discrete brain structures of rats were different, the greatest retention of amphetamine accompanied by relative increase in

glucose utilization⁽¹¹⁾. The increased NADH would cause a decrease of cerebral adenosine triphosphate (ATP) requirement, resulting in an increase of $(ATP)/[(ADP) \times (HPO_4^{2-})]$ ratio and a decrease of oxygen consumption^(10,12). It is possible that amphetamine during electroshock on the rat's foot increased the levels of NADH concentrations in majority of brain structures, resulting in a decrease of NAD/NADH ratio, an increase of $(ATP)/[(ADP) \times (HPO_4^{2-})]$ ratio as well as an increase of utilization of glucose. It is worth to test the supposition in future.

There was a linear increment of activity with caffeine doses ranging from 25 to 150 mg/kg in the mice⁽⁶⁾. In our experiment, jumps of rats with caffeine (120 mg/kg ip) were increased for 3 min, but it decreased from the 3rd min to the 5th min. The NADH concentrations in the studied brain structures were increased at the 3rd min, but it were decreased at the 5th min. The phase changed in NADH concentration was discovered in the studies about microwave effects on energy metabolism of rat^(13,14). These meant that caffeine caused a phased change in NADH concentration of rat brain, it potentiated jumps in the experimental tube for a short period (3 min).

REFERENCES

- 1 Frackowiak RSJ, Pozzilli C, Legg NJ, *et al.* Regional cerebral oxygen supply and utilization in dementia. *Brain* 1981; 104 : 753
- 2 Mazziotta JC, Phelps ME, Kuhl DE, Packwood J. Tomographic mapping of human cerebral metabolism : auditory stimulation. *Neurology* 1982; 31 : 921
- 3 Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: sensory deprivation. *Ann Neurol* 1982; 12 : 435
- 4 Shen Z, Lin SZ. Brain NADH and jumping behavior in the rat. *Life Sci* 1985; 37 : 731
- 5 Lal H, Marky M, Feilding S. Effects of neuroleptic drugs on mouse jumping induced by amphetamine treated mice. *Neuropharmacology* 1976; 15 : 669

- 6 Knoll J. Motimeter a new sensitive apparatus for the quantitative measurement of hypermobility caused by psychostimulants. *Arch Int Pharmacodyn Ther* 1961; 130 : 141
- 7 Iversen SD, Iversen LL. *Behavioral pharmacology*. 2nd ed. NY: Oxford University Press. 1981 : 154
- 8 Konig JFR, Klippel RA. *The rat brain—a stereotaxic atlas*. 1st ed. Baltimore: Williams & Wilkins, 1963 : 23-157
- 9 Rawat AK, Kuyriama K, Mose J. Metabolic consequences of ethanol oxidation in brain from mice chronically fed alcohol. *J Neurochem* 1973; 20 : 23
- 10 Lamanna JC, Younts BW, Rosenthal M. The cerebral oxidative metabolic response to acute ethanol administration in rats and cats. *Neuropharmacology* 1977; 16 : 283
- 11 Eison MM, Eison AS, Ellison G. The regional distribution of *d*-amphetamine and local glucose utilization in rat brain during continuous amphetamine administration. *Exp Brain Res* 1981; 43 : 281
- 12 Wilson DF, Stubbs M, Veech RL, Ericinska M, Krebs HA. Equilibrium relations between the oxidation reductions and the ATP synthesis in suspensions of isolated liver cells. *Biochem J* 1974; 140 : 57
- 13 Sanders AP, Schaefer DJ, Joines WT. Microwave effects on energy metabolism of rat brain. *Bioelectromagnetics* 1980; 1 : 171
- 14 Sanders AP, Joines WT. The effects of hyperthermia and hyperthermia plus microwaves on rat brain energy metabolism. *Ibid* 1984; 5 : 63

中国药理学报 1987年3月; 8(2): 97-100

苯丙胺与咖啡因对大鼠跳跃行为及脑还原型辅酶 I 的影响

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提要 本文从脑区域性代谢的角度, 以 40 只大鼠为材料研究了苯丙胺(1.5 mg/kg)和咖啡因(120 mg/kg)对跳跃行为与脑还原型辅酶 I (NADH)的影响。苯丙胺增强大鼠在足底电击时的跳跃行为, 同时增加额叶皮层、海马、尾状核、间脑和小脑五个脑结构内的 NADH 浓度。咖啡因在实验的前 3 min 增加六个脑区

的 NADH 浓度与大鼠跳跃行为, 但这种效应很快逆转, 在 5 min 时全部脑区的 NADH 含量及跳跃行为显著降低。

关键词 苯丙胺; 咖啡因; 跳跃行为; 辅酶 I; 海马; 小脑; 尾状核; 间脑; 额叶皮层