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Behavioral and Neurochemical Effects of Caffeine in Normal and Aggressive Mice[1]

L. VALZELLI AND S. BERNASCONI

Istituto di Ricerche Farmacologiche, Mario Negri, Via Eritrea 62, 20157 Milan, Italy

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VALZELLI, L. AND S. BERNASCONI. *Behavioral and neurochemical effects of caffeine in normal and aggressive mice.* PHARMAC. BIOCHEM. BEHAV. 1(3) 251–254, 1973.–Caffeine is known to exert psychostimulant effects both in man and in animals and it has been shown to modify the levels of brain neurotransimitters. In normal and isolated-aggressive mice, caffeine induces modifications of both the level and the turnover of brain serotonin. Such modifications are however more evident in normal than in aggressive mice. Moreover, caffeine shows an antiaggressive effect and increases the exploratory activity of aggressive mice, without altering the performance of normal animals. It seems possible to conclude that the biochemical and behavioral effects of this drug differ in extent and intensity depending upon the emotional baseline on which it acts.

Caffeine Aggressiveness Exploratory behavior Brain serotonin level and turnover

THE PSYCHOSTIMULANT effects of caffeine in man have been well known for several years, and its action may be modulated by such factors as individual differences in sensitivity [11] or previous habitual or occasional drinking habit [5]; in such a manner psychomotor coordination, alertness, and mood may be differentially influenced by caffeine administration [12]. Similar differences in the effects of caffeine have also been demonstrated in laboratory animals as dependent upon age and sex [17], reduced food intake [15] and the type of diet [16,18].

Moreover, it has recently been reported that caffeine administration leads to increases in the serotonin (5-HT) concentration of the brain stem and of 5-hydroxyindoleacetic acid (5-HIAA) content in the brain [1], in such a way as to suggest that 5-HT may play a role in the pharmacological activity of this drug [2].

Furthermore, increased norepinephrine (NE) synthesis in the brain stem [3], as well as a decrease in brain 5-HT and dopamine (DA) turnover have been described [6].

Based upon the observation that prolonged isolation in mice induces aggressiveness [22,29] as well as alterations in exploratory behavior [23], differential sensitivity to drugs as compared with normal animals [26,27], and changes in brain 5-HT turnover [9, 20, 25], the present paper deals with the effects of caffeine on brain monoamines and several behavioral meausres, including isolation-induced aggressiveness and exploratory activity in differentially housed mice.

METHOD

Male Swiss Albino mice, weighing 20 ± 2.0 g, were housed, either eight per cage or isolated in individual Makrolon cages for 28 days at a constant room temperature of 22°C and 60% relative humidity and were fed ad lib. The aggressive behavior of these animals was tested on the twenty-ninth day after differential housing by grouping three previously isolated mice and evaluating the intensity of fighting within a five minute interval according to a scale previously reported [21,28].

This procedure was carried out at several different times following the intraperitoneal (i.p.) administration of either 0.9% saline or several different doses of caffeine, while exploratory activity was measured at several postdrug treatment times using the "Hole-board test" [4, 23, 24].

Brain 5-HT and 5-HIAA concentrations were determined simultaneously for the same individual tissue samples according to the method of Giacalone and Valzelli [10] and brain 5-HT turnover was calculated according to a steady-state kinetics procedure [19], with monoamine-oxidase activity being blocked with tranylcypromine (20 mg/kg i.p.). As an initial procedure, the effect of caffeine on brain 5-HT and 5-HIAA levels (100 mg/kg i.p.) was studied at different times following its administration to normal and aggressive mice.

RESULTS AND DISCUSSION

The effects of caffeine upon brain 5-HT and 5-HIAA

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level (Table 1) are consistent with those reported for rats by Berkowitz and Spector [1]; the present data indicate, however, a more prolonged period wherein the 5-HT and 5-HIAA levels are elevated in the brain of aggressive mice as compared with normal ones. This finding suggests differences in the magnitude of the effect of caffeine on brain 5-HT turnover in the two types of animals, which show per se, as previously described [20,25] a significant difference in this metabolic measure. Caffeine induced a decrease in brain 5-HT turnover in both aggressive and in normal mice (Table 2); this was, however, more significantly pronounced (38%) in the latter than in the former animals (23%) (x^2 = 3.90; df = 1; $p<0.05$). Caffeine exerted an effective and long-lasting anti-aggressive effect, even at very low doses (Table 3), and this apparently paradoxical effect may, in some respects resemble that produced by methylphenidate under the same test conditions [28], as well as by amphetamines on the hyperactive behavior of children and adults [14]. Moreover, caffeine exerted differential effects on the exploratory behavior of normal and aggressive mice; the latter explored less than normal controls, to the point of being completely inactive (blocked aggressive mice) [24]. The results observed with other psychoactive drugs [24] have been summarized in Table 4.

TABLE 1

THE EFFECTS OF CAFFEINE (100 MG/KG, I.P.) UPON BRAIN LEVEL OF 5-HYDROXYTRYPTAMINE (5-HT) AND 5-HYDROXYINDOLACETIC ACID (5-HIAA) IN NORMAL (N) AND AGGRESSIVE (A) MICE AT DIFFERENT TIMES AFTER ADMINISTRATION

Treatment	Time after administration (min)	Brain content (μg/g ± S.E.)			
		5-HT		5-HIAA	
		N	A	N	A
Saline	–	0.61 ± 0.02	0.61 ± 0.02	0.32 ± 0.01	0.29 ± 0.01
Caffeine	30	0.68 ± 0.04	0.71 ± 0.02*	0.40 ± 0.02†	0.36 ± 0.03*
	60	0.68 ± 0.03	0.71 ± 0.01*	0.39 ± 0.01†	0.43 ± 0.02†
	120	0.70 ± 0.02*	0.70 ± 0.02*	0.52 ± 0.03†	0.48 ± 0.03†
	240	0.67 ± 0.02	0.60 ± 0.02	0.46 ± 0.03†	0.46 ± 0.03†

Each figure corresponds to the mean of 8 animals ± S.E.
* = $p<0.05$
† = $p<0.01$

TABLE 2

EFFECT OF CAFFEINE (100 MG/KG, I.P.) ON THE BRAIN 5-HYDROXYTRYPTAMINE (5-HT) TURNOVER IN NORMAL (N) AND AGGRESSIVE (A) MICE

Treatment	Brain 5-HT turnover			
	Rate (μg/g/hr)	% Variation	Time	$K^{(h-1)}$
N + saline	0.55	–	61	1.54 ± 0.08
N + caffeine	0.34*	38%	107	0.80 ± 0.02*
A + saline	0.35	–	97	1.25 ± 0.05
A + caffeine	0.27*	23%	138	0.74 ± 0.03*

* = $p<0.01$
Each figure corresponds to the mean of 8 animals.

TABLE 3

EFFECTS OF CAFFEINE UPON ISOLATION-INDUCED AGGRESSIVE BEHAVIOR IN MICE AT DIFFERENT DOSES AND POST-TREATMENT TIMES

Time after administration (min)	Caffeine (mg/kg i.p.)							
	Saline		5		10		20	
	L	A	L	A	L	A	L	A
10	0	100	0	75	0	75	0	50
20	0	100	0	100	0	75	0	50
60	0	100	20	50	0	25	10	25*
120	0	100	25	50	180	0*	40	25*
240	0	100	10	25	25	25*	10	25*
480	0	100	15	50	180	0	15	25
1440	0	100	40	50	0	25	10	25
1920	0	100	20	75	0	50	15	25
2880	0	100	5	75	0	75	5	50

Each figure corresponds to the mean of 6 animals.
L = Latency time (sec) of attacking.
A = Aggressiveness intensity
* = Hyperexcitation

TABLE 4

EFFECT OF CAFFEINE (20 MG/KG I.P.) ON THE EXPLORATORY BEHAVIOR OF NORMAL (N) AND AGGRESSIVE (A) MICE

Treatment	Time after administration (Hr)	Number of holes explored ± S.E. N	A Active	A Blocked
Saline	0	30 ± 2	12 ± 1	1
	1.5	20 ± 4	10 ± 2	0
	8	27 ± 3	7 ± 2	0
	24	22 ± 3	8 ± 2	1
	48	23 ± 5	7 ± 3	1
Caffeine	0	29 ± 3	11 ± 1	1
	1.5	23 ± 6	4 ± 1*	9 ± 4*
	8	16 ± 6	5 ± 2*	3 ± 2
	24	14 ± 8	3 ± 2*	5 ± 3
	48	8 ± 4*	4 ± 1*	4 ± 2

Each figure corresponds to the mean of 8 animals ± S.E.
* = $p < 0.01$ in respect to 0 time.

It is of interest to observe that caffeine, similar to other psychotropic agents, modulated its action according to the emotional level of the animals considered, without any appreciable alteration of the exploratory behavior of the normal mice at the dose employed; furthermore, this drug reduced exploratory behavior in mice showing active aggression and provided for improved performance in animals showing blocked aggression. Such differential behavioral effect of caffeine was also observed in rats, wherein increased locomotor activity was reported [7], except for those animals in which the pre-drug activity level was spontaneously high [13].

In conclusion, caffeine, as has been reported in other rodents [1, 2, 6], has also been shown to modify brain levels of 5-HT and 5-HIAA in mice, and provides for a decrease in brain 5-HT turnover. This effect, however, just as the behavioral effects of this drug, differs in intensity and extent depending upon the emotional baseline upon which it is superimposed; this consideration has also been described in man [11,12].

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