Discussion. The findings reported explain on the one hand why elevated concentrations of PG are demonstrable in the cerebrospinal fluid in the course of febrile reactions due to the release of EP[5,19]. On the other hand, in so far as PG can be considered to serve as mediators of the pyrogenic effects of EP, the observed activation of cerebral PGSS by EP would explain this mechanism of action. It must be borne in mind, however, that the concentration of arachidonic acid is a rate-limiting step in the chain of enzymatic reactions leading to the biosynthesis of PG. The question thus arises whether the pyretic effect of EP is solely the result of its influence on cerebral PGSS, or whether other mechanisms may also be involved[20].

In contrast to the activity of cerebral PGSS, that of PGSS isolated from seminal vesicles was not affected by EP. This disparity could be connected with the fact that the PGSS in various tissues are isoenzymes[21]. The possibility cannot, however, be excluded that the different susceptibilities of the PGSS isolated from the cerebral cortex and the seminal vesicle may only be due to variations in the isolation conditions. The finding that the cerebral PGSS displays less enzymatic activity than PGSS from seminal vesicles favours this assumption.

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Mescaline: its Effects on Learning Rate and Dopamine Metabolism in Goldfish (*Carassius auratus*)[1]

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Summary. The pharmacological action of mescaline on goldfish was studied with the Bitterman-Agranoff shock-avoidance test. In short term experiments with high mescaline doses an increase in learning rates was observed. Similar results were obtained with apomorphine and L-dopa. However, when the fish were exposed to smaller mescaline doses (or to fluphenazine) for 3 days, their ability to avoid electric shock was reduced. Apparently, mescaline induced a release of dopamine which stimulated central dopaminergic systems. Subsequently, MAO destroys the liberated dopamine. Thus, the ensuing dopamine deficit appears to be responsible for the marked changes in behavior in the chronic experiment.

It has been reported that the clinical symptoms in man and animals induced by mescaline can be reversed by injection of chlorpromazine[2] and that mescaline is capable of releasing cerebral dopamine[3]. These and other observations suggest the involvement of a dopaminergic system in mescaline action. If this were true, monoamine oxidase (MAO, EC 1.4.3.4), should be a part of this reaction by destroying the liberated dopamine. To test this conjecture we exposed goldfish to mescaline. We already had extensively studied the influence of modulators of amine metabolism on the behavior and cerebral amine metabolism of goldfish[4]. As in the past, we used the modified Bitterman-Agranoff shock avoidance test[5]. The fish are electrically shocked when they do not clear a submerged barrier within 10 sec after a light signal is turned on. This response is recorded as an error. 30 trials, given every 30 sec, form 1 training period which is repeated on 2 consecutive days. Each set of controls or test animals was comprised of at least 6 fish. When we plotted the logarithm of the number of errors for 5 consecutive trials, for all fish, against the number of trials (1st to 5th, 6th to 10th, etc.), a linear function characterized by high correlation coefficients ($r \leq 0.9$) emerged[4]. This observation makes it possible to tabulate the results numerically and to gain simple and strictly operationally defined behavioral parameters, e.g. slope (SL) of straight lines serving as a convenient indicator of learning rate. Here, the term of learning pertains to the totality of physiological processes which are responsible for behavioral changes in repeat performances.

In contrast to the outcome of experiments with hundreds of control animals, the slope of the linear function obtained for mescaline-treated fish always became positive for the second and more so for the third trial period (Table). The animals were increasingly unable to initiate movements in order to avoid electric shock although their capacity to move appeared to be completely intact. The pharmacologically inactive analogues of mescaline, viz. 3,4,5-trimethoxybenzylamine and 2,3,4-trimethoxy-β-phenylethylamine did not react in our system. The mescaline effect seems to be due to a lack of cerebral dopamine as indicated by the following observations reported in the Table: a) the behavioral changes are accompanied by a marked drop in brain dopamine levels while the content of norepinephrine and serotonin remained constant; b) application of several inhibitors of MAO, e.g. deprenyl, or of L-dopa abolished both the behavioral and metabolic mescaline effects; c) the dopaminergic antagonist, fluphenazine, evoked the same behavioral response as mescaline; again L-dopa administration prevented this reaction. In contrast, the treatment of the animals with L-dopa or with the dopaminergic agonist apomorphine led to higher learning rates. These responses made it pos-

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Action of mescaline (mesc) alone or in combination with other agents affecting catecholamine action and metabolism

Treatment	Day 1 SL	Day 2 SL	Day 3 SL	MAO (μmoles/h)	Monoamines (μg)		
					DA	NE	5HT
Controls	— 4.0 ± 1.9	— 8.0 ± 4.7	— 8.3 ± 4.1	5.8	2.15 ± 0.07	0.46 ± 0.02	0.35 ± 0.05
Mesc (10^{-5} *M*)	— 5.8 ± 0.4	2.2 ± 1.0	19.6 ± 10.0	5.4	1.28 ± 0.01	0.44 ± 0.01	0.31 ± 0.01
Controls	— 3.0	— 4.0	— 2.0		1.50 ± 0.02	0.47 ± 0.01	0.53 ± 0.01
Mesc (10^{-4} *M*, 3 h/day)	— 10.0	— 14.0	— 21.0		1.91 ± 0.02	0.60 ± 0.01	0.52 ± 0.01
L-dopa (10^{-4} *M*)	— 9.0	— 12.6	— 17.0	5.3	2.17	0.48	
Mesc (10^{-5} *M* + dopa)	— 10.0	— 11.2	— 10.8	5.8	1.96	0.43	
Deprenyl (10^{-6} *M*)	— 31.4	— 34.9	— 35.6	0.1	2.75		
Mesc (10^{-6} *M* + depren.)	— 4.0	— 9.6	— 13.0	0.1	2.87		
Fluphenazine (10^{-6} *M*)	— 3.0	5.0	22.0	7.9	1.94	0.45	
Fluph. + dopa (10^{-4} *M*)	— 3.4	— 8.0	— 14.4	7.1			
Apomorphine (10^{-6} *M*)	— 14.2	— 24.8	— 21.6	3.9	2.47	0.52	

The MAO activity was measured with 10^{-3} *M* tyramine; the hydrogen peroxide produced in this reaction converted homovanillic acid into a fluorescent compound in the presence of horse radish peroxidase[11]. The cerebral amines were determined after 3 and 72 h of exposure of the fish to the drugs; after extraction they were converted to fluorescent compounds with *o*-phthaldialdehyde (5HT) or iodine (DA, NE)[12]. MAO activities and amine levels were calculated for 1 g of fresh brain. The standard deviations were computed on the basis of data obtained for 18–36 fish, except monoamine determinations (6 fish). All groups, with the exeption of the second one, were exposed to the drugs for 24 h a day. Abbreviations: SL, slope of the linear relationships as defined in the text; DA, dopamine; NE, norepinephrine; 5HT, serotonin.

sible to differentiate 'short' and 'long' mescaline exposure: when we exposed the fish to a much higher concentration of mescaline for only 3 h prior to the training period, the slopes of the linear functions were significantly more negative than those obtained from controls ($p < 0.005$) and almost identical with those resulting from L-dopa application; no decrease in dopamine levels occurred. Thus, the phenomena recorded for short and long exposures to mescaline are dramatically different.

Our conclusion that dopamine – either derived from administered L-dopa or released by mescaline – is capable of increasing learning rate does not stand alone, as the following examples show: in rats, L-dopa improved learning in conditioned avoidance tests[6] while in mice the same drug reversed impaired learning due to the destruction of the dopaminergic nigrostriatal projection[7]. In a long series of studies, initiated by Arbit, et al.[8] and reviewed and extended by MURPHY, L-dopa was found to enhance learning in parkinsonian and non-parkinsonian patients.

To illustrate the second, mescaline-induced dopamine deficient state, few unambiguous data can be found in the literature, apparently because the distinction between the 'acute' and 'chronic' states has not been made before. Muscle rigidity and tremor observed in dogs and monkeys after the administration of very large doses of mescaline may suggest a dopamine loss[9].

Many times, similarities between mescaline-produced syndromes and certain schizophrenic reactions have been noted[2]. Since hyperactivity of a dopaminergic system is thought to be involved in the pathogenesis of (paranoid) schizophrenia (as discussed by SNYDER et al.[10]), abnormally high cerebral dopamine levels may be the common denominator of acute mescaline action and some schizophrenic symptoms. This concept throws some light on many earlier observations[2], e.g. on the reversal of mescaline responses by phenothiazines.

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Effects of Morphine Administration on Cerebellar Guanosine 3′,5′-Monophosphate

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Summary. An increase in mouse cerebellar C-GMP levels during acute morphine treatment was observed, which was possibly related to the decrease in C-GMP phosphodiesterase levels also observed in acute treatment. Chronic treatment lowered C-GMP levels as did abrupt withdrawal without naloxone.

Although a role for adenosine 3′,5′-monophosphate in morphine dependence has been tentatively described[1,2] the involvement of guanosine 3′,5′-monophosphate (C-GMP) is less well understood. BONNET[3] has reported significant reduction in C-GMP levels in rat caudate, substantia nigra, hypothalamus, and thalamus with acute morphine injections in both normal and morphine pelleted animals. However, TRABER et al.[4] have found that acute opiate exposure of neuroblastoma × glioma hybrid cells elevated intracellular C-GMP levels. To clarify the