Mice infected with live Coxsackievirus B3 or B4 and killed on the 18th day of gestation weighed less than control animals and occasionally exhibited slightly staring coats and mild oedema of the head and neck regions. Macroscopical and histological changes noted in the liver and pancreas were similar to those described previously[1,2]. They included hepatocellular vacuolation and a degeneration and atrophy of pancreatic exocrine tissue with an infiltrate of mono-nuclear and plasma cells.

At autopsy, the stomach and upper regions of the intestinal tract of infected animals appeared normal and did not differ macroscopically from the controls. However, the ileum, caecum and upper colon appeared to be dilated and oedema of the lamina propria was identified histologically. Although the villi in the duodenum and ileum were normal in height and displayed a characteristic pattern of mucus secreting and absorptive cells, the tips of these villi were frequently swollen with the lamina propria assuming a pebble-like appearance with histological features of a lymphangiectasia as described by WHITEHEAD[9]. Mononuclear and plasma cells were present in the lamina propria in the duodenum, ileum, caecum and colon but were only slightly more numerous than in the control animals. In many instances these increases in infiltrated cells were focal. In the caecum and colon profound oedema was present with a marked dilatation of the gut lumen associated with a thinning and distension of the mucosae. Focally the mucosa was reduced to a single layer of cuboidal cells with few mucus secreting cells and poorly defined basement membrane. Occasionally this condition was accompanied by an increased number of mononuclear and plasma cells.

Previous studies in mice infected with Coxsackievirus B3 have shown that in animals infected on day 8 of pregnancy, signs of pancreatic exocrine insufficiency and protein deficiency were identified 4 days later[2]. This means that in animals killed on the 18th day, the period of nutritional stress is short and the intestinal changes of oedema and focal mucosal atrophy consistent with a short period of protein deficiency. One might expect that if these animals were examined at a later stage after infection, more severe symptoms of protein deficiency including partial or sub-total villous atrophy in the small intestine, oedema and pronounced inflammatory cell infiltration of the type reported by SHINER et al.[7] would have been noted. Lymphangiectasia which seems to be a characterisitic feature of intestinal changes in acute protein deficiency and malabsorption syndromes[6,9] was also present in these animals and would seem to be an early manifestation of the condition.

The exact implications of these intestinal changes upon the state of health of the pregnant mother or on the development of the fetuses at 18 days gestation is unclear. In view of the evidence presented that only in advanced cases of protein deficiency resulting from several months deprivation where villous atrophy is well advanced, is the absorptive capacity of the gut altered[8,10]; it seems unlikely therefore that the early intestinal changes present in these Coxsackievirus infected mice at the stage examined present any appreciable risk to the health of the pregnant mothers. One might speculate that intestinal changes of a more advanced type which may be reasonably expected, at a later stage, after infection, may have adverse effects on health of the animals and on the developmental pattern in the fetuses.

Zusammenfassung. Bei graviden, mit Coxsackie-Virus B3 infizierten Mäusen war der obere Darmabschnitt im Vergleich mit den Kontrolltieren makroskopisch unverändert. Im Ileum, Coecum and Colon ascendens war bei einer Dilatation ein Oedem der Lamina propria mit Zellinfiltrat vorhanden, während die Mucosa vereinfacht war. Ein Zusammenhang mit Pankreasveränderungen wird als möglich angenommen.

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Lysergic Acid Diethylamide Affects Blood Flow to Specific Areas of the Conscious Rat Brain

There are few neurophysiological clues to areas in the nervous system which are responsive to lysergic acid diethylamide (LSD) in spite of recent evidence of binding of this hallucinogen in the brain[1,2]. As a means of screening the various areas of the brain whose functions might be altered by such compounds we have studied the regional perfusion of the nervous system in conscious, unrestrained rats.

The utility of this approach is based upon the assumption that 1. functional and, therefore, metabolic activity determines, in large part, the flow of blood to nervous tissues[3–8] and 2. that functional changes elicited by drugs in various parts of the brain are sufficiently large so as to provoke changes in blood flow which are detectable by our method.

Materials and methods. A relatively convenient method, described elsewhere[9], was used to simultaneously measure the flow of blood to each of 10 regions in the brains of conscious, unrestrained male rats. The method is our updating of the Sapirstein indicator-fractionation technique which can utilize a number of lipid soluble isotopic indicators such as thiopental-^{14}C (unpublished observations), ^{131}I-iodoantipyrine, or as employed here, antipyrine-^{14}C. Under the conditions of these experiments, when such an indicator is administered in a single i.v. injection and the killing time is short, then the pattern of antipyrine distribution in the brain is the same as the fractional distribution of the cardiac output.

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Table I. Effects of LSD on regional brain blood flow in the rat as a function of time after i.v. injection (0.3 mg/kg)

Tissue	Control	Time after LSD	
		10 min	20 min
Cerebellum	0.88 ± 0.02	0.94 ± 0.04	1.00 ± 0.02 [c]
Pons and medulla	0.79 ± 0.02	0.82 ± 0.03	0.85 ± 0.02
hypothalamus	0.84 ± 0.02	0.86 ± 0.04	0.87 ± 0.02
Basal ganglia	0.85 ± 0.02	0.92 ± 0.03	0.91 ± 0.02
Midbrain	0.89 ± 0.02	0.88 ± 0.04	0.92 ± 0.02
Dorsal hippocampus	0.74 ± 0.02	0.69 ± 0.03	0.69 ± 0.02
Olfactory bulb	0.76 ± 0.02	0.80 ± 0.03	0.82 ± 0.02
Cortex, frontal	0.98 ± 0.03	1.11 ± 0.05 [a]	1.11 ± 0.03 [c]
parietal	1.01 ± 0.03	1.17 ± 0.06 [b]	1.15 ± 0.02 [c]
occipital	0.99 ± 0.03	0.97 ± 0.04	0.94 ± 0.02
Cardiac output (ml/min/kg)	367 ± 15	357 ± 18	351 ± 11
Arterial blood			
pH	7.42 ± 0.02	7.41 ± 0.01	7.39 ± 0.01
P_{CO_2} mm Hg	41 ± 1	38 ± 2	42 ± 1
P_{O_2} mm Hg	85 ± 2	84 ± 2	76 ± 1 [c]
Number of animals	22	10	15

Flow values are expressed as means ± S.E., ml/min · g. [a] $P < 0.025$; [b] $p < 0.01$; [c] $p < 0.001$.

The method employed here permits the estimation not only of the fractional distribution of the cardiac output but also the minimum absolute flow of blood which exchanges nutrients with a given region. All studies were performed on 73- to 83-day-old male Wistar rats. On the day of measurement, and either isotonic saline or LSD, 300 µg/kg in 1 ml of isotonic saline solution, was injected slowly into catheters implanted three days earlier; equivalent weights of the 2-methyl, 6-nor, or $\Delta^{8,9}$ LSD derivatives were similarly prepared and administered. In the case of LSD, flow measurement commenced 10 or 20 min later; effects of the LSD derivatives were determined 20 min after injection. Regional blood flow was measured employing a standard protocol which has been described in detail previously[9].

Results. LSD – Table I. In general, all animals appeared somewhat aroused during the first 10 min after injection of LSD, as evidenced by increased sniffing and grooming. During this time blood pressure was elevated typically about 15 mm Hg above mean preinjection levels of 118 mm Hg; however, cardiac output was unchanged. By 20 min after LSD administration, when behavioral effects were maximum, animals were much less active, more apprehensive, and often appeared to be staring fixedly into space; nevertheless, they would orient quickly to a sharp sound. Blood pressure at this time had returned to preinjection levels and cardiac output was again unchanged.

At the time when behavioral effects of LSD were still minimal but cardiovascular effects were maximal, i.e., 10 min, perfusion of most regions of the brain was slightly but consistently elevated and flows to frontal and parietal cortex were significantly increased, 13 and 15%, respectively. Hippocampal flow, on the other hand, was reduced slightly. By 20 min when the full behavioral effects were evident, cerebellar, as well as frontal and parietal flows were significantly elevated and flows to the occipital cortex and hippocampus were slightly depressed. No

Table II. Differential effects of LSD and some derivatives on regional brain blood flow in the male rat 20 min after i.v. injection

Tissue	Control	LSD	2-methyl LSD	6-Nor-LSD	$\Delta^{8,9}$-LSD
			(0.3 mg LSD equivalent/kg)		
Cerebellum	0.88 ± 0.02	1.00 ± 0.02 [c]	0.85 ± 0.07	0.92 ± 0.05	0.91 ± 0.04
Pons and medulla	0.79 ± 0.02	0.85 ± 0.02	0.74 ± 0.06	0.80 ± 0.04	0.80 ± 0.03
Hypothalamus	0.84 ± 0.02	0.87 ± 0.02	0.79 ± 0.07	0.87 ± 0.04	0.87 ± 0.02
Basal ganglia	0.85 ± 0.02	0.91 ± 0.02	0.80 ± 0.07	0.89 ± 0.05	0.86 ± 0.03
Midbrain	0.89 ± 0.02	0.92 ± 0.02	0.86 ± 0.07	0.92 ± 0.04	0.92 ± 0.03
Dorsal hippocampus	0.74 ± 0.02	0.69 ± 0.02	0.70 ± 0.06	0.76 ± 0.05	0.75 ± 0.03
Olfactory bulb	0.76 ± 0.02	0.82 ± 0.02	0.66 ± 0.06 [a]	0.75 ± 0.04	0.75 ± 0.03
Cortex, frontal	0.98 ± 0.03	1.11 ± 0.03 [c]	0.93 ± 0.06	0.96 ± 0.04	0.99 ± 0.04
parietal	1.01 ± 0.03	1.15 ± 0.02 [c]	0.95 ± 0.07	1.06 ± 0.06	1.03 ± 0.04
occipital	0.99 ± 0.03	0.94 ± 0.02	0.97 ± 0.09	0.99 ± 0.05	1.03 ± 0.04
Cardiac output (ml/min/kg)	367 ± 15	351 ± 11	379 ± 15	276 ± 17 [b]	382 ± 21
Arterial blood					
pH	7.42 ± 0.02	7.39 ± 0.01	7.42 ± 0.01	7.40 ± 0.01	7.42 ± 0.01
P_{CO_2} mm Hg	41 ± 1	42 ± 1	41 ± 1	41 ± 1	40 ± 1
P_{O_2} mm Hg	85 ± 2	76 ± 1	99 ± 1	83 ± 2	90 ± 2
Number of animals	22	15	8	8	7

Flow values are expressed as means ± S.E., ml/min · g. [a] $P < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

subcortical structures were affected significantly. Thus, the gross behavioral alterations were preceded by changes in regional perfusion, which became less variable and more pronounced with time. Blood gases were unaffected at 10 min after injection of LSD although a slight hypoxia was observed by 20 min.

LSD derivatives – Table II. The 2-methyl-LSD, 6-nor-LSD and $\Delta^{8,9}$-LSD derivatives failed to alter rat behavior in any observable way at a dose level which was markedly effective in the case of LSD; in additional subgroups of animals behavioral effects were not detected beyond 40 min after i.v. injection. Furthermore, the 2-methyl and $\Delta^{8,9}$ derivatives also failed to alter blood pressure or cardiac outputs. The 6-nor-LSD, however, appeared more potent in mimicking the peripheral effects of LSD by elevating arterial pressures by about 40 mm Hg above mean pressures and significantly reducing cardiac outputs by 25%. None of these compounds affected regional perfusion of the brain, with the possible exception of 2-methyl LSD which caused a fall in olfactory bulb flow.

Discussion. The flow changes to the parietal and frontal cortex, cerebellar and, perhaps, the dorsal hippocampal regions appear to be related to the behavioral effects. The findings with 2-methyl LSD, 6-nor LSD, and $\Delta^{8,9}$ LSD to which rats are not visibly responsive, reveal no changes in regional perfusion of the brain, although some of these compounds have considerable peripheral cardiovascular effects (Table II). Assuming as other do[3–8] then, that regional blood flow in the brain is secondary to function, the most parsimonious explanation for these findings is that the flow changes signal net increases in the activities of the parietal, frontal, and cerebellar cortices of the rat at the same time that some functions of the dorsal hippocampus perhaps decrease. In past studies in conscious men[10] and anesthetized cats[11] gross cerebral perfusion appeared unchanged by LSD administration. That LSD, indeed, increased the flow of blood to certain areas of the brains of conscious rats emphasizes our contention that these relatively restricted responses were the result of tissue activity responses likely to be obscured by whole brain measurements or the use of anesthetics[9].

Although the changes in regional perfusion of the brain may signal changes in function, the primary sites of action of LSD remain obscure. Some regions which retain radiolabelled LSD have been interpreted as possible sites of action[1]. Thus, accumulations of LSD in those mesencephalic and diencephalic structures associated with autonomic centers in the brain correlate well with the centrally mediated autonomic effects of the drug[12]. Although LSD also binds selectively to a minority of cells in frontal cortex and cerebellum[1,2], regions to which the flow of blood also is increased, the widespread uptakes of LSD in many subcortical areas are not paralleled by flow changes. Along with the acknowledged effects in subcortical regions then, the flow data suggest that some cortical regions and cerebellum also are responsive to LSD. At this time, however, it is impossible to distinguish between secondary functional aspects and primary sites of drug action[13].

Zusammenfassung. Die i.v. Verabreichung von LSD an Ratten steigert den Blutkreislauf im Hirnstamm sowie im frontalen und parietalen Cortex selektiv. Es wurden durch 6-Nor-LSD, 2-Methyl-LSD und $\Delta^{8,9}$-LSD weder wahrnehmbare Verhaltensänderungen noch Änderungen des regionalen Blutkreislaufs verursacht.

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Inhibition of Prostaglandin Synthetase by Psychotropic Drugs

According to the hypothesis advanced by VANE, the pharmacodynamic activity of non-steroidal anti-inflammatory agents (NSAA's) is attributable to the inhibition of prostaglandin (PG) synthetase[1–3]. It therefore seemed of interest to determine whether this effect is peculiar to this class of compounds. With this end in view, and in the light of recently published observations indicating that certain psychotropic agents may interfere with PG synthesis[4,5], we undertook experiments to find out whether compounds possessing neuroleptic, antidepressant and/or tranquillizing properties, inhibit PG synthetase in vitro.

Material and methods. The enzymatic assay was carried out according to a modification of the technique described by TAKEGUCHI et al.[6]. The incubation medium contained 3 mg of the lyophilized microsomal fraction of bovine seminal vesicle as enzyme, 0.33 μM ^{14}C-labelled arachidonic acid (spec. activity: 58 mCi/mM) and 9.85 μM unlabelled arachidonic acid as substrate, and 2.95 mM l-adrenaline and 2.93 mM reduced l-glutathione as cofactors in 5 ml *Tris* buffer at pH 8.3. Each of the compounds tested was added to the reaction mixture in three different concentrations. After incubation for 30 min, the reaction was stopped by the addition of one drop of concentrated hydrochloric acid, and the lipid fraction extracted twice with ethyl acetate and separated by thin-

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