Les résultats que nous avons obtenus sont rassemblés dans les Tableaux I et II dans lesquels nous avons fait figurer, à titre de comparaison, les valeurs obtenues par BLANC et al.[14] sur la lactotransferrine et par SCHULTZE et al.[27] sur la transferrine. Ils peuvent être résumés de la manière suivante:

(1) La composition en glucides et en acides aminés de la lactotransferrine et de la transferrine humaines présente des différences significatives. En outre, la transferrine possède la valine en position N-terminale comme l'avaient déjà démontré PUTNAM[28], ERIKSSON et al.[29] et SCHULTZE et al.[30], tandis que nous n'avons pas mis en évidence d'acide aminé N-terminal dans la lactotransferrine.

Ces résultats expliquent la spécificité immunologique de la lactotransferrine[8,9,12,14]. Il est intéressant, à cet égard, de souligner que GORDON, GROVES et BASCH[31] parviennent à la même conclusion à propos de la lactotransferrine et de la transferrine bovines.

(2) Dans un premier travail[13], nous avions déterminé la composition en acides aminés de la lactotransferrine par la méthode des DNP-aminoacides de LEVY[32] et les résultats que nous avions obtenus étaient les suivants (en moles d'amino-acides par mole de lactotransferrine): acide aspartique 92, acide glutamique 76, arginine 53, histidine 16, lysine 51, alanine 95, $^1/_2$ cystine 30, glycocolle 72, leucine et isoleucine 96, phénylalanine 36, proline 43, sérine 60, thréonine 37, tyrosine 9, valine 61. On voit que, pour la plupart des amino-acides, les résultats fournis par les méthodes de LEVY, d'une part, et de MOORE et STEIN, d'autre part, sont très voisins, mais qu'il existe cependant d'importantes différences pour certains d'entre eux, comme l'acide aspartique, l'alanine, le glycocolle, la valine et, principalement, la tyrosine. Ces anomalies peuvent s'expliquer par l'imperfection de la méthode de LEVY.

D'autre part, les résultats que nous a fournis l'application de la méthode de MOORE et STEIN à la détermination de la composition en amino-acides de la lactotransferrine et de la transferrine sont pratiquement identiques à ceux, respectivement, de BLANC et al.[14] et de SCHULTZE et al.[27].

Summary. A comparative study of human lactotransferrin and transferrin has been made with respect to sugar and amino acid composition. The authors conclude that there are significant differences between both types of glycoproteids, which confirm the specificity of lactotransferrin previously demonstrated by physico-chemical and immunological analysis.

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Evidence for a Direct Action of Monamines on the Chick Central Nervous System

The presence of the blood-brain barrier prevents the entry of significant amounts of systematically injected biogenic amines (norepinephrine and serotonin) into the brain of most adult vertebrates[1,2]; therefore the elucidation of the central nervous system (CNS) functions of these amines is difficult. Present concepts of the functions of the monamines are based primarily upon indirect evidence obtained by alteration of the normal indole- and catechole-amine metabolic pathways, rather than by observation of direct effects of these amines on the CNS. The young chick appears to be a preparation in which the direct effects of the monamines on the CNS can be observed since systemically administered catechole- and indole-amines of pharmacological importance appear to traverse the blood-brain barrier[3,4]. In spite of this immature barrier, the CNS of the chick possesses adult characteristics and responds to neuropharmacological agents in a manner similar to most mammals[4].

In the present experiments, the electrical activity of the brain and gross behavior were examined prior to, and after the administration of, the various biogenic amines in order to provide direct evidence of the pharmacological effects of these monamines. These experiments were performed on over one hundred unrestrained, unanesthetized chicks (5–14 days old). Electroencephalographic (EEG) recording electrodes[5] were implanted in the corpus striatum of the chick anesthetized with nitrous oxide. Following recovery from the anesthesia, the animals were placed in a sound attenuated, behavioral observation box. Blood pressure was monitored in some of the preparations[6]. The EEG and behavioral effects of the indole- and catecholeamines and their precursors were examined.

The indoles studied were 5-hydroxytryptamine (5-HT) administered subcutaneously as the creatinine sulfate

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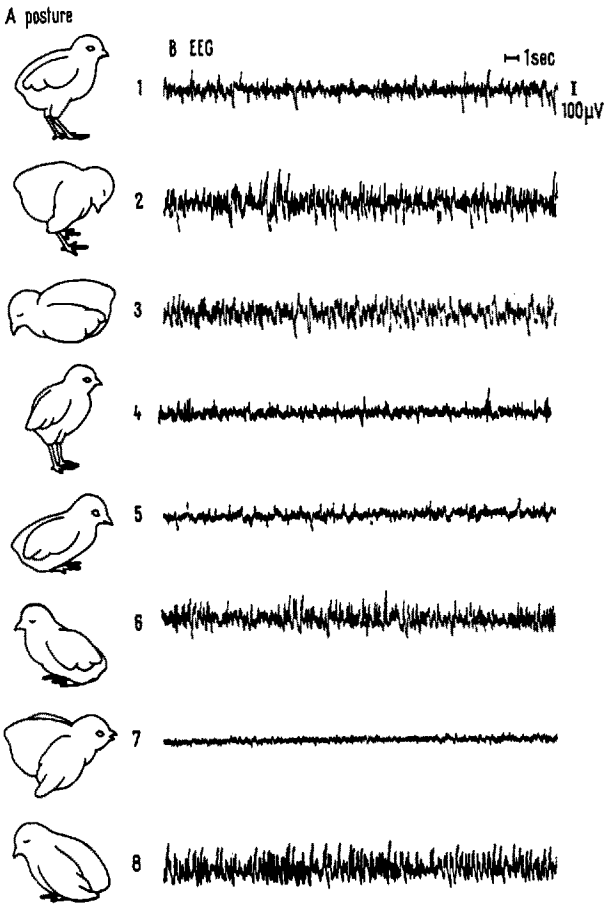
complex, and the amino acid precursor 5-hydroxytryptophan (5-HTP) administered intraperitoneably. The studies confirm the reported observation that 5-HT, 0.1–20 mg/kg, produces EEG and behavioral signs of sleep in young chicks[4,7] (Figure: 2, 3). After a latent period of 25 to 50 min, the amino acid precursor 5-HTP, 50–180 mg/kg, produces EEG and behavioral signs of sleep similar to those induced by 5-HT (Figure: 2, 3) presumably via a metabolic conversion to 5-HT. These results (summarized in the Table) suggest that 5-HT does enter the CNS of the young chick and that these direct effects result in CNS depression.

The catecholes examined were the amino acid precursor *d-l*, dihydroxyphenylalanine (DOPA), dopamine hydrochloride (DA), and *l*-norepinephrine bitartrate (NE). Following a 10–20 min latency, DOPA 50–300 mg/kg i.p. produces an alert EEG; the animal is wide-eyed, nonvocal and akinetic (Figure : 4). A monamine oxidase inhibitor, iproniazid phosphate, 100 mg/kg i.p., administered 15 h before the experiment, prolongs the duration of the alerting effects of 50–100 mg/kg of DOPA to 3–4 times that of comparable doses of DOPA alone. The latency of onset (10–20 min) and the potentiation of the effect by a monamine oxidase inhibitor, suggests that an amine product and not DOPA produces the alerting effect. Higher doses of DOPA, 200–400 mgm/kg i.p., administered to chicks pretreated with iproniazid, produces the same sequence of alerting effects but after 30 min the EEG and behavior change to a sleep-like pattern. The biphasic effect of the higher doses of DOPA combined with iproniazid are similated by the administration of DA, 75–100 mgm/kg i.p. (Figure: 4–6). Following DA there is a rapid change in the EEG to an alert pattern and the animal appears alert, nonvocal and akinetic; however, within 30 min EEG and behavioral patterns of sleep appear. After the administration of NE, 0.05–4.0 mg/kg s.c., there is a rapid appearance of EEG and behavioral signs of sleep (Figure: 2, 3) in confirmation of previously reported studies[3,4,8].

The results summarized in the Table suggest that in this preparation: (1) the arousal effects observed after DOPA result from a metabolic conversion of the precursor to DA; (2) the late depressive responses observed after DOPA (200–400 mg/kg) plus iproniazid, and also after the administration of DA alone, are probably caused by the synthesis and subsequent overflow of NE formed from the precursor DA; and finally, (3) that as was noted with 5-HT, both DA and NE introduced into the systemic circulation can enter the CNS of the young chick, since these amines produce effects that are identical to, but more rapid in onset than, their respective amino acid precursors which are known to enter the brain.

The effects noted following these amines cannot be explained on the basis of a blood pressure effect. A previous study in chicks clearly demonstrated that the EEG and behavioral effects of systemically administered monamines are drug specific and not related to changes in the blood pressure[6]. Nor can these findings be attributed to a species difference since the central nervous system of the chick responds in a manner similar to that of the higher vertebrates to compounds such as amphetamine, chlorpromazine, and reserpine[4,8]. Administration of *d-l*, amphetamine sulfate, 2.5–10 mg/kg s.c., produces EEG and behavioral arousal in the young chick (Figure: 7). Prominent signs of EEG and behavioral depression are evident in the chick 30 min after chlorpromazine hydrochloride, 25–100 mgm/kg i.p., or reserpine phosphate, 1–10 mgm/kg i.p. (Figure: 8). In the light of this evidence, a reinterpretation of the interaction of amphetamine, chlorpromazine, and reserpine with the biogenic amines is in order. Since NE induces EEG and behavioral sleep-like patterns, while amphetamine induces patterns of excitation, it does not seem likely that amphetamine is mimicking NE in the CNS. The central effects of NE and amphetamine have been demonstrated to be antagonistic to each other in the young chick[8]. This evidence plus the structural similarity of the two compounds suggest that amphetamine may act via a block of the depressive effect of endogenous NE in the CNS.

Based mainly on peripheral and also indirectly obtained CNS evidence, the central actions of chlorpromazine have been postulated to be due to a blocking action on NE in



Postural and EEG responses in chicks. The chick outlines (A) are representative of the posture and the EEG tracings (B) observed during normal and drug induced responses. The EEG records are monopolar recordings from the hyperstriatum (reference electrode at the base of the comb). The postures outlined and the EEG tracings are representative of: (1) normal awake; (2) and (3) normal sleeping, or 30 min after 5-hydroxytryptophan (5-HTP), or immediately after 5-hydroxytryptamine (5-HT), or norepinephrine (NE); (4) 1/2 h after dihydroxyphenylalanine (DOPA) or immediately following dopamine (DA); (5) 15 min after DA; (6) 1/2 h after DA; (7) following *d,l*-amphetamine sulfate; and (8) the depressive phase of either chlorpromazine HCl or reserpine phosphate. See the text for respective doses of drug.

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EEG and behavioral effects of the biogenic amines in the chick

Substance	Dose mg/kg	Injection route	EEG pattern	Behavior	Remarks
5-Hydroxytryptophan	50–280	i.p.	Sleep	Sleep-like	Latency to onset (25–50 min)
5-Hydroxytryptamine	0.1–20	s.c.	Sleep	Sleep-like	Rapid onset (2 min)
Dihydroxyphenylalanine	50–300	i.p.	Alert	Alert but akinetic	Latency to onset (10–20 min)
Dihydroxyphenylalanine + Iproniazid[a]	50–100	i.p.	Alert	Alert but akinetic	Latency to onset (20–50 min). Duration 3–4 × DOPA alone
Dihydroxyphenylalanine + Iproniazid[a]	200–400	i.p.	Alert followed by sleep	Alert followed by sleep-like	Latency to onset (15–20 min). Sleep-like state 30 min after onset of alert EEG
Dopamine	75–100	i.p.	Alert followed by sleep	Alert followed by sleep-like	Rapid onset of arousal followed by sleep-like state after 30 min
Norepinephrine	0.05–4.0	s.c.	Sleep	Sleep-like	Rapid onset (2 min)

[a] Iproniazid PO_4, 100 mg/kg i.p., 15 h pre-experiment.

the CNS[9]. The present and more direct evidence outlined in this study does not support this concept, but rather indicates that chlorpromazine exerts CNS effects by mimicking or potentiating the action of NE and perhaps other biogenic amines. This is substantiated in part by the close resemblance of the chick response to chlorpromazine and the NE response, or the late effects observed after DA.

The action of reserpine has been proposed to be mediated by the blockade of monamine storage sites[10]. The present results suggest that the reserpine depression may be caused by newly synthesized and unbound NE or 5-HT overflowing on receptor sites, since systemic injection of NE or 5-HT alone, or in combination, produces a state of depression that is similar to the reserpine induced state.

In summary, this report presents pharmacological evidence that: (1) 5-HT, DA and NE appear to enter the CNS of the young chick; (2) 5-HT and NE produce EEG and behavioral patterns of sleep; (3) DA or its precursor DOPA produce an initial akinesia, plus EEG and behavioral signs of arousal. These direct data are discussed in terms of a re-evaluation of several mechanisms of action of the psychotropic drugs whose actions are believed to be mediated via an interaction with the biogenic amines[11].

Zusammenfassung. Pharmakologische Untersuchungen im Hinblick auf eine eventuelle Wechselwirkung von psychotropen Pharmaka und biogenen Aminen ergaben: (1) offenbares Eindringen von 5-HT, DA und NE in das Zentralnervensystem junger Hühner. (2) Schlafcharakteristisches Verhalten von EEG und Verhaltensweise nach Verabreichung von 5-HT und NE. (3) Auftreten der «arousal»-Charakteristika mit anfänglicher Akinese im EEG und Verhalten nach Dopamin- oder Dopazufuhr.

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On the Presence of Mucopolysaccharide Material in the Labyrinthine Epithelium of Chick Embryo in the First Moments of Morphogenesis

The morphogenesis of the cupula ampullaris and of the otolithic membrane is still a somewhat obscure problem in the development of the membranous labyrinth[1–5]. Already during the course of previous studies, we have had occasion to classify the mucopolysaccharides that enter into the formation of these structures from the histochemical point of view. Our investigations[6] brought to light the non-uniform nature of the mucopolysaccharides

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