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Serine and Glycine-Induced Catalepsy in Porphyric Rats: An Animal Model for Psychosis?

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SCHOUTEN, M. J., J. BRUINVELS, L. PEPPLINKHUIZEN AND J. H. P. WILSON. *Serine and glycine-induced catalepsy in porphyric rats: An animal model for psychosis?* PHARMACOL BIOCHEM BEHAV 19(2) 245–250, 1983.—It was investigated whether an increased demand for glycine, as postulated to occur in patients who have suffered from episodic psychoses accompanied by multiple perceptual distortions, could evoke psychotic reactions. Catalepsy was used as a measure for psychosis and was observed after injection of serine or glycine in porphyric rats. Catalpesy was shown to occur after serine as well as glycine administration in 2-allyl-2-isopropylacetamide (AIA) pretreated rats, while in lead (Pb) + phenobarbital pretreated rats only glycine was effective. Administration of AIA to rats resulted in a strongly enhanced excretion of porphobilinogen (PBG) in urine, while Pb + phenobarbital pretreated rats showed increased excretion of δ-aminolevulinic acid (δ-ALA). The Pb + phenobarbital pretreated animals showed elevated serine plasma levels and lowered glycine plasma levels 18 hours after injection, while no significant differences in plasma levels of these amino acids were found 24 hours after AIA administration. In AIA or saline pretreated animals, but not in those pretreated with Pb + phenobarbital, glycine formation from serine was elevated. It is concluded that the present animal model can be used to investigate episodic psychoses.

Serine Glycine Porphyria Porphyrinogenic agents Catalepsy Tetrahydro-β-carbolines Tetrahydroisoquinolines Psychosis Catatonia Perceptive disorders

IT has been generally accepted that the effects of hallucinogens in man bear a large resemblance to the symptoms of an acute psychosis. During the past two decades many suggestions have been made about the possible endogenous formation of hallucinogenic or even "schizophrenic" compounds. Osmond and Smithies [22] were the first to postulate that a false methylation of catecholamines may form a biological basis for schizophrenia.

It has been suggested previously that an increased production of $CH_2{=}FH_4$ and not CH_3-FH_4 could be involved in the development of schizophrenia [6]. Under physiological conditions this compound can be non-enzymatically decomposed into FH_4 and formaldehyde (HCHO) [11] of which the latter can react spontaneously via the Pictet-Spengler reaction with indolamines or catecholamines forming THβC's or THIQ's respectively [1, 10,19]. This suggestion was supported by the findings of Pearson *et al.* [23] that, *in vitro*, serinehydroxymethyl transferase (SHMT) is capable of forming THβC from tryptamine. This enzyme converts serine into glycine and concomitantly, FH_4 into $CH_2{=}FH_4$. As has been postulated recently, an overproduction of $CH_2{=}FH_4$, caused by an increased demethylation of serine, could evoke a schizo-affective, mescaline-like psychosis. This type of acute psychosis is characterized at the onset by multiple sensory perceptual distortions, hallucinations, affective symptoms and finally culminating into catatonic states. The typical hallucinogenic drug-like symptoms could be evoked by oral administration of serine and in a few cases by glycine in a dose of 2 mmol/kg or by the consumption of food containing large amounts of serine and glycine. In 20% of these patients also porphyria was detected. This supports our hypothesis, since the high demand for glycine during a porphyric attack will be met by demethylation of serine by the action of SHMT [7,24]. As pointed out above, the concomitantly formed $CH_2{=}FH_4$ could be responsible for the production of THβC's or THIQ's via the Pictet-Spengler reaction.

The present study was undertaken to investigate the possibility of an animal model in order to obtain more information about the postulate that an increased production of $CH_2{=}FH_4$ during increased conversion of serine into glycine, may be responsible for the induction of psychosis.

ABBREVIATIONS

$CH_2{=}FH_4$	N_5,N_{10}-Methylenetetrahydrofolic acid
CH_3-FH_4	N_5-Methyltetrahydrofolic acid
FH_4	Tetrahydrofolic acid
THβC	Tetrahydro-β-carboline
THIQ	Tetrahydroisoquinoline

METHOD

A total number of 54 male albino Wistar rats (125–150 g) was used in the present study. Per experiment rats were divided into 3 groups of three rats. Six experiments were performed. Rats were starved for 24 hr before the injection of the porphyrinogenic agents.

Induction of Porphyria

Injection of lead acetate + phenobarbital. One group of three rats was injected with 25 mg/kg (IV) lead acetate (Merck) dissolved in 0.25 ml glass-distilled demineralized water (demidest) and 50 mg/kg (IP) phenobarbital-sodium salt (Gist-Brocades) in 0.5 ml 0.9% NaCl [18].

Injection of 2-Allyl-2-isopropyl acetamide (AIA). A second group of three rats was injected with 400 mg/kg AIA (SC, a gift from Hoffman La Roche) [15] dissolved in 1 ml polyethylene glycol (J. T. Baker Chemicals). A control group of three rats received polyethylene glycol. The rats were placed in metabolic cages (Acme Metal Products, Chic., IL,USA) immediately after injection of the porphyrinogenic agents for separate collection of urine and feces.

Administration of Serine or Glycine

At maximum porphyria, which was 18 hr after injection of Pb + phenobarbital [18] and 24 hr after injection of AIA [15] one rat in each group received serine, glycine (both from Aldrich, 2 mmol/kg in 0.5 ml 0.9% NaCl) or saline, respectively (IP).

Catalepsy

Catalepsy was measured once before injection of serine, glycine or saline, and at 5, 10, 20, 30 and 60 minutes after injection of the amino acid. The catalepsy measurements were performed by placing the rat on a vertical grit with a grit size of 1.5×1 cm, about 10 cm above the cage floor. The time the animal did not displace one of his front- or hind paws out of this position was recorded. Catalepsy was scored as follows:

time (sec)	score
0	0
0–10	1
10–20	2
20–30	3
>30	4

To detect statistical differences Students' *t*-test was performed using the total scores of each rat representing the sum of catalepsy scores measured in duplo at 5, 10, 20, 30 and 60 minutes after injection of amino acid.

Excretion of δ-Aminolevulinic Acid (δ-ALA) and Porphobilinogen (PBG) in the Urine

δ-ALA and PBG in the urine were determined according to Doss *et al.* [12] with some modifications. Urine was collected in dark brown collection bottles which were acidified in advance with 100 μl 100% acetic acid in order to keep the urine, 0.55 g cationex change material (Ag 50 WX4 100–200 PBG (both from Sigma Chemical Co.), 3×0.5 cm ion-exchange columns were used. To extract δ-ALA from the urine, 0.55 g cationex-change material (Ag 50 WX4 100–200 mesh, H^+-form, Bio-Rad) was used. PBG was extracted with 0.55 g anionexchanger (Ag 1X8 100–200 mesh, acetate form, Bio-Rad). The columns were rinsed with 10 ml deionized water before use. The thawed urine samples were adjusted between pH 6.0 and 6.5 with solid $NaHCO_3$ just before 0.5 ml of urine was loaded onto each column. The columns were rinsed with 3×10 ml deionized water, and PBG was eluted with 2×2 ml 1 M acetic acid, while δ-ALA was eluted with 5+2 ml 1 M Na-acetate. Acetylaceton (0.2 ml) (Merck) was added to the δ-ALA eluates which were incubated for 10 min at 100°C to convert δ-ALA into a pyrrolic compound. To detect the pyrrolic compounds 2 ml of each PBG column eluate or each δ-ALA incubate was mixed with 2 ml Ehrlich's reagent (100 ml 2.4% (w/v) p-dimethylaminobenzaldehyde in 100% acetic acid mixed with 19 ml 70% $HC10_4$). This mixture was incubated for 15 min at 37°C and extinction was measured at 553 nm.

Determination of Serine and Glycine Plasma Levels

Blood samples were taken every 2 min before measurement of catalepsy by cutting a small slice from the tail. Fifty μl of blood was taken into heparinized capillaries. The capillaries were centrifuged for 11 min at 12000 rpm (15000×g) in a Haemofuge (Heraeus). Plasma was separated by cutting the capillaries just above the layer of erythrocytes and transferred on a piece of Parafilm and diluted with 4 volumes of elution buffer A as used in HPLC (see below). This mixture was incubated at 4°C for 60 min and solid particles were spun down in a Beckman Microfuge for 5 min at 9000×g. Subsequently 10 μl of supernatant was injected into a Hewlett Packard Liquid Chromatograph 1084 B equipped with a 20 cm Li-Chrosorb RP-8 (5 μm) column (Hewlett Packard). Serine and glycine were determined by using a "Dynamic Ion Exchange" system [14] with some modifications: Eluens A consisted of 0.5% sodiumdodecyl sulphate (SDS, Merck, w/v) 0.5 mM sodiumcitrate, 0.3% t-amylalcohol (v/v) and was adjusted at pH 3.20 with citric acid. Eluens B consisted of 0.5% SDS (w/v), 10 mM Na_3PO, 0.3% t-amylachol (v/v) and was adjusted to pH 7.9 with H_3PO. Serine and glycine were eluted with buffer A at a flow rate of 2.4 ml/min at 40°C, followed by 4 min buffer B and 10 min buffer A at the same flow rate and temperature to elute the slower compounds and those not of interest and to equilibrate the column for the next analysis, respectively. The amino acids were detected by postcolumn derivatization with o-phthaldialdehyde (OPA, Merck) at ambient temperature using a mixing chamber connected to the end of the analytical column. A Duramat Dosing pump (Chemie and Filter GmbH, Verfahrenstechnik K.G., Heidelberg 1), which was set at a flow rate of 2.4 ml/min was used to pump the OPA-reagent into the mixing chamber. Fluorescence was measured 3 sec afterwards in an Aminco SPF 500 ratio fluorimeter using an excitation wavelength of 337 nm (bandwith 10 nm) and an emission wavelength of 452 nm (bandwith 40 nm). The OPA-reagent was prepared by dissolving 0.5 g OPA in 10 ml ethanol and mixing with 2 ml 2-mercaptoethanol (sol. I). 1 1.3% H_3PO_3 (w/v) was adjusted to pH 10.2 with NaOH pellets (sol. II) [9]. Sol. I and sol. II were mixed and kept under nitrogen in dark brown bottles. Under these conditions, the reagent was stable for two weeks [9].

RESULTS

Porphyria

The induction of porphyria was shown by measuring the excretion of δ-aminolevulinic acid (δ-ALA) and porphobilinogen (PBG) in the urine. In rats made porphyric by the injection of Pb + phenobarbital δ-ALA excretion per 48 hr was about 28× increased as compared to the excretion by

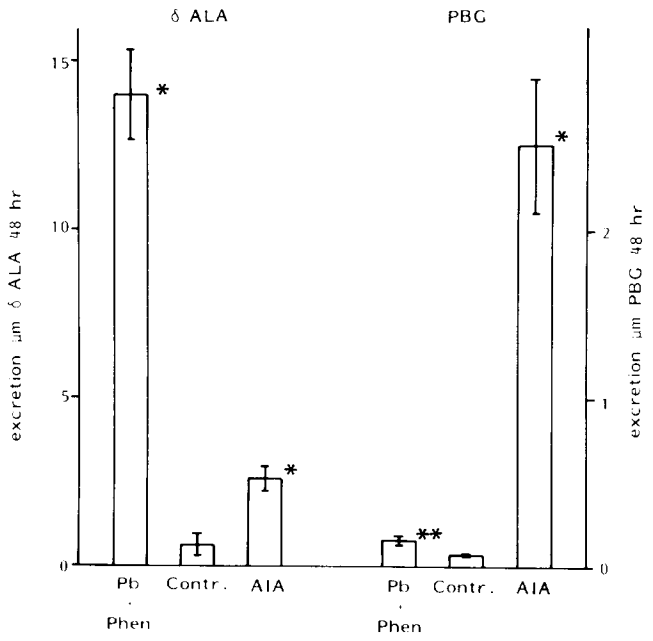

FIG. 1. Excretion of δ-aminolevulinic acid (δ-ALA) and porphobilinogen (PBG) in the urine during 48 hr after injection of Pb + phenobarbital or AIA. $*p<0.001$;$**p<0.005$ (Student t-test).

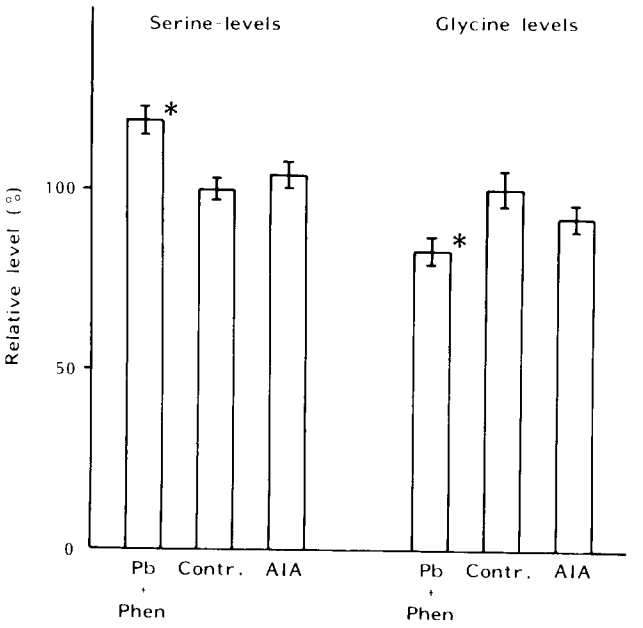

FIG. 2. Serine and glycine blood plasma levels during porphyria. These levels were measured 24 hr after injection of AIA and 18 hr after injection of Pb + phenobarbital respectively, and before injection of serine or glycine. $*p<0.005$ (Student t-test). Control serine and glycine plasma levels were 404 (±13) μmol/l and 527 (±24) μmol/l respectively.

non-porphyric control rats, while PBG excretion per 48 hr in these rats was twice the amount of control rats. The AIA pretreated rats showed an opposite pattern: PBG excretion in these animals was about 35× the amount excreted by non-porphyric controls, while δ-ALA excretion was increased by a factor 4 as compared to controls (Fig. 1).

As shown in Fig. 2, blood serine and glycine levels were changed in Pb + phenobarbital pretreated rats. Plasma serine levels were significantly elevated 18 hr after injection of Pb + phenobarbital, while glycine levels were significantly lowered. No significant differences in plasma serine and glycine levels were obtained in AIA pretreated animals measured 24 hr after injection of AIA.

No changes in urinary excretion of δ-ALA and PBG could be found as a consequence of serine or glycine administration in both porphyric and control rats.

As shown in Fig. 3, a negative, semilogarithmic correlation between δ-ALA excretion and plasma glycine levels was found using the data obtained from porphyric and control rats before treatment with serine or glycine.

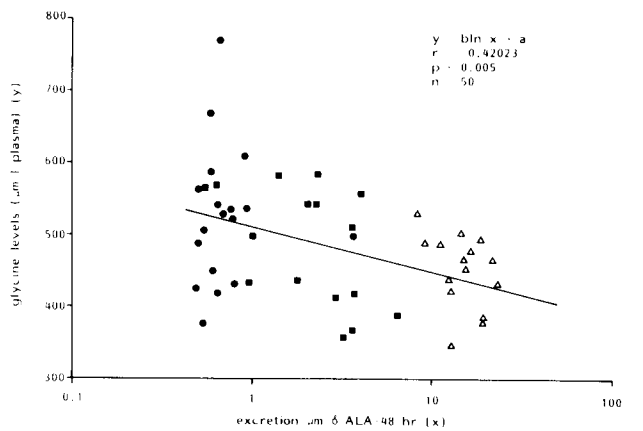

FIG. 3. Semilogarithmic correlation between excretion of δ-ALA during 48 hr in the urine and glycine blood plasma levels after pretreatment, measured 24 hr after injection of AIA (■) or saline (●), and 18 hr after injection of Pb + phenobarbital (△).

Serine and Glycine Administrations

Injection of glycine into Pb + phenobarbital pretreated rats did not increase serine plasma levels (Table 1a), while in AIA pretreated animals serine levels were elevated 20–60 min after glycine injections as compared to AIA pretreated, saline injected controls. Only at 30 min after glycine administration to saline pretreated rats significantly elevated serine levels could be found. Comparable results were obtained for the conversion of serine into glycine, indicating no detectable conversion in Pb + phenobarbital or saline pretreated rats but an increased conversion in AIA-pretreated rats 20 min after injection of serine (Table 1b).

Catalepsy Scores

Administration of serine or glycine to AIA pretreated rats evoked catalepsy after administration of either amino acid as shown in Table 2. However, in Pb + phenobarbital pretreated rats, only administration of glycine caused catalepsy. No catalepsy was found in rats pretreated with Pb + phenobarbital or AIA alone nor could it be shown after ad-

TABLE 1A

SERINE LEVELS IN PORPHYRIC RATS INJECTED WITH SERINE OR GLYCINE

Pretreatment	inj. amino acid	Time in min (control level) 0	20	30	60
PB + phenobarbital	serine	100* (± 8.1)	175.5 (± 4.9)	178.2 (± 8.3)	151.7 (± 3.8)
	glycine	100 (± 8.4)	106.1 (± 6.1)	104.7 (± 6.5)	103.5 (± 4.2)
	saline	100 (± 4.2)	90.5 (± 3.0)	92.0 (± 2.7)	91.8 (± 3.7)
AIA	serine	100 (± 8.6)	207.3 (±11.0)	190.2 (± 6.5)	160.4 (± 4.4)
	glycine	100 (± 7.9)	103.5‡ (± 2.0)	103.1‡ (± 3.6)	98.6‡ (± 3.8)
	saline	100 (± 3.7)	90.9 (± 2.6)	85.0 (± 3.0)	82.6 (± 2.8)
saline	serine	100 (±11.5)	187.0 (±13.7)	183.2 (±15.1)	156.1 (±11.2)
	glycine	100 (± 4.2)	100.9 (± 5.1)	101.6 (± 4.1)†	93.5 (± 5.1)
	saline	100 (± 5.4)	93.7 (± 1.9)	89.8 (± 2.1)	86.8 (± 2.1)

*Mean as percent of control level (±S.E.M.) of 6 rats.
†$p<0.05$, ‡$p<0.01$ (Student t-test, amino acid injected vs. saline injected in the same pretreated group at indicated time).

TABLE 1B

GLYCINE LEVELS IN PORPHYRIC RATS INJECTED WITH SERINE OR GLYCINE

Pretreatment	inj. amino acid	Time in min (control level) 0	20	30	60
Pb + phenobarital	serine	100* (±6.3)	92.1 (± 3.3)	96.2 (± 3.7)	96.3 (± 2.7)
	glycine	100 (±4.3)	302.1 (±32.9)	303.5 (±30.7)	218.9 (±17.9)
	saline	100 (±3.7)	93.6 (± 2.6)	91.7 (± 1.4)	87.0 (± 4.1)
AIA	serine	100 (±6.9)	102.0† (± 3.7)	97.2 (± 2.3)	102.4 (± 4.9)
	glycine	100 (±8.6)	268.4 (±31.9)	229.9 (±13.6)	193.7 (± 6.7)
	saline	100 (±4.0)	96.7 (± 1.7)	93.2 (± 1.4)	96.1 (± 2.0)
saline	serine	100 (±8.2)	90.1 (± 2.0)	95.0 (± 3.2)	100.7 (± 5.2)
	glycine	100 (±7.2)	249.2 (±22.8)	239.6 (±14.5)	167.8 (± 6.2)
	saline	100 (±4.5)	92.5 (± 5.2)	94.4 (± 1.5)	91.9 (± 2.2)

*Mean as percent of control level (±S.E.M.) of 6 rats.
†$p<0.02$ (Student t-test amino acid injected vs. saline injected in the same pretreated group at indicated time).

ministration of serine or glycine in non-pretreated rats. Most of the cataleptic rats also exhibited widely opened eyelids and stiffness of the tail (Straub tail).

DISCUSSION

To enhance the demand for glycine, porphyria was chemically induced in rats, which were starved 1 day before treatment. For this purpose, injection of 2-allyl-2-isopropylacetamide (AIA) was used as one method and administration of lead (Pb) + phenobarbital as the other [15, 18, 30].

Administration of AIA resulted in massive excretion of PBG per 48 hr in the urine. AIA quite specifically acts as a porphyrinogenic agent by accelerating the breakdown of heme, which is the feedback inhibitor of the heme pathway, and heme proteins, thereby inducing the activity of δ-aminolevulinic acid synthetase (δ-ALAS) [15, 29, 30]. This enzyme will produce large amounts of δ-ALA, which is quickly converted into porphobilinogen (PBG) [16]. In order to meet this massive production of δ-ALA glycine synthesis has to be increased since the latter is one of the two substrates for δ-ALAS.

Both Pb and phenobarbital are slightly porphyrinogenic. When injected simultaneously however they have a strong potentiating effect [18]. Our results revealed a 28× increase of δ-ALA excretion in the urine during 48 hr, indicating the induction of δ-ALAS, which is in agreement with the findings of Maxwell *et al.* [18].

The present results show that glycine levels are correlated with δ-ALA excretion into the urine in both types of porphyria (Fig. 3), probably because the demand for glycine is

TABLE 2
CATALEPSY SCORES IN PORPHYRIC RATS

Pretreatment	inj. amino acid	total scores	(±SEM)
Pb + phenobarbital	serine	9.3*	(±1.7)
	glycine	16.7†	(±1.6)
	control	11.1	(±3.7)
AIA	serine	10.0	(±2.8)
	glycine	10.0	(±1.6)
	control	8.7	(±1.7)
control	serine	19.8‡	(±1.0)
	glycine	17.0§	(±2.6)
	control	9.8	(±2.8)

*Mean of total catalepsy scores (representing the scores measured at 5, 10, 20, 30 and 60 min after amino acid injection) obtained from 6 rats.

†$p < 0.02$ vs. glycine injected, non-pretreated rats.

‡$p < 0.01$ vs. serine injected, non-preteated rats.

§$p < 0.05$ vs. glycine injected, non-pretreated rats. Statistical differences were measured by applying Student's t-test.

enhanced. Because most of the glycine pool is synthesized from serine via serinehydroxymethyl transferase (SHMT) [4,21], increased serine levels in Pb + phenobarbital pretreated rats are not expected to occur together with the enhanced need for glycine in porphyria. Probably SHMT is inhibited by lead, which can react with the sulfhydryl groups at the active site of SHMT [20,26]. This would explain both the lowered glycine levels and increased serine levels in Pb + phenobarbital pretreated rats.

Different types of animal behaviour can be used as an indication for psychotic behaviour [5, 13, 17, 28]. Among these, catalepsy and catatonia are the most frequently used [5, 17, 27]. Although these terms are often used interchangeable, they have dissimilar behavioural profiles and may imply different categories of participating neurotransmitter systems [8]. The difference between the rigid- and non-rigid-type of immobility (catatonia and catalepsy, respectively) is based on the findings obtained with opiate-like drugs and the behaviour seen after neuroleptic drug treatment. According to Segal *et al.* [27], the vertical grid test, as used in the present study, measures catalepsy. However, some of our cataleptic rats also showed stiff tails and wide-opened eyelids, which is suggestive for catatonia [27]. Therefore, both serine and glycine probably evoked cataleptic as well as catatonic behaviour, which may be comparable to the catatonic behaviour shown by some of our patients [24].

The observation that serine, when injected into Pb + phenobarbital pretreated rats could not evoke catalepsy, while glycine did, is in agreement with the proposed inhibition of SHMT by Pb as discussed above. This would also explain the increased glycine plasma levels in Pb + phenobarbital pretreated, glycine injected animals (Table 1b).

The finding that glycine can evoke catalepsy would not appear to fit in with our hypothesis that the elevated conversion of serine into glycine gives rise to high levels of $CH_2{=}FH_4$. However, high amounts of glycine can be metabolized in the glycine cleavage system (GCS) to CO_2 and NH_3, concomitantly forming $CH_2{=}FH_4$ from FH_4. As pointed out above, increased levels of $CH_2{=}FH_4$ could be intermediates in alkaloid production.

Tetrahydro-β-carbolines (THβC) and tetrahydroisoquinolines (THIQ) can be formed from indoleamines and catecholamines respectively and formaldehyde, formed by decomposition of $CH_2{=}FH_4$. The possibility that formaldehyde-derived biogenic amines can act as psychotogenic or "schizophrenic" agents, is suggested by many authors [2, 10, 25]. Especially THβC's, which are derived from indoleamines, received much attention, as reviewed by Airaksinen *et al.* [2,3].

Studies are in progress to isolate and identify the compounds responsible for inducing catalepsy in rats. These compounds may also be responsible for evoking episodic psychosis in patients.

In conclusion, catalepsy could be evoked during experimental porphyria in rats after injection of serine and glycine, and may probably represent a good model for studying a schizophrenic-like psychosis as described previously [7,24]. The AIA-induced porphyria seems to be more suitable for further experimentation, because this drug acts in a more specific way on the heme pathway.

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