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Original Research

Effect of Combined Prenatal Exposure to Aluminium and Ethanol on Central Dopamine, Serotonin and Muscarine Receptor Reactivity in Rats

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Abstract

Ethanol (EtOH) abuse in pregnancy is know to seriously damage the internal organs of the fetus, a condition in humans that is classified as "fetal alcohol syndrome". Aluminium (Al) can develop neurotoxic effects and contribute to some neurological disorders. To test whether the reactivity of some central receptors (dopamine - DA, serotonin-5-HT and muscanne - M) may be altered by prenatal EtOH and Al, administered separately or jointly, female rats were given 10% (v/v) EtOH and/or Al(600 or 3000 ppm) throughout pregnancy in their drinking water. Male adult offspring were tested at 3 months for behavioural effects know to be induced by agonists acting at different subtypes of DA (D_1, D_2, D_3), 5-HT_{2c} and M receptors. Addition antagonist of D_2 receptor have been examined. The substances SKF 38393, quinpirole, mCPP, pilocarpine, haloperidol, and the behavioral procedures of yawning, oral activity and catalepsy have been used for assessment.

The results of the experiment indicate that EtOH does not modify the effect of the central DA and M receptor agonist and DA antagonist in Al prenataly exposed rats. On the other hand, EtOH modified the reactivity of the central 5-HT_{2c} receptor to agonist (mCPP) in Al pretreated rats.

Keywords: ethanol, aluminium, rats, prenatal, SKF 38393, quinpirole, mCPP, pilocarpine, haloperidol, behaviour

Introduction

Aluminium (Al) is widespread in the natural human environment. Large amounts of Al are found in the earth, air and water. Generally its concentration in natural water is negligible due to its insolubility in normal weathering conditions. However, the acidification of water as the result of industrial development has caused an increase in Al concentration. In addition, the salts of Al are used in foods, cosmetics and in medicine. The calculated amount of Al ingested to be in the range of 1-100 mg/day, with an average of 20 mg/day, but only about 1 mg is absorbed [29]. Preparing, boiling or storaging drinks or foods with low pH in Al kitchen utensils can dissolve a significant amount of the metal [34, 41].

The first reports of Al neurotoxic effects in animals appeared in the '30s [47]. Later, others showed that Al salts administered to mammals (rabbits, cats) caused neurofibrillary changes in the motor neurons of the

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spinal cord as well as in other neurons of the medulla and cerebral cortex, which were accompanied by seizures or learning deficits [16, 51, 52]. In the '70s it was shown that Al plays a major role in the development of dialysis encephalopathy in patients with renal insufficiency [3]. This disease is characterized by speech difficulties, EEG changes, dementia, myoclonus and seizures. Encephalopathy was reported in Al factory workers who had been exposed to dust heavily contaminated with Al [27, 36]. From this the connection between Al content of the brain and various dementias has been determined. Following reports of elevated levels of Al in the brain of patients with Alzheimer's disease, ADHD (Attention Deficit Hyperactivity Disorder) and individuals with dialysis dementia, Al was proposed as an aethiological or pathogenic factor in the above-mentioned disturbances [2, 4, 14, 17, 18, 28, 35, 50, 53, 54]. On the other hand, the role of Al in the pathogenesis of Alzheimer's disease is questionable [21].

One of the most characteristic biochemical symptoms of Alzheimer's disease is the generally diminished function of the central cholinergic system [15]. Al in animal experimental models influenced acetylcholine synthesis, storage and transport in the brain [13, 25, 26, 37]. In addition some data exist that other central neurotransmitter systems (serotoninergic, noradrenergic, GABA-ergic, glutaminergic, peptidergic) are changed in the brains of animals intoxicated with Al. Previously, we found that prenatal and long-term postnatal exposure of rats to Al damage the central dopaminergic system in rats [42].

Ethanol (EtOH) is another xenobiotic which cause serious damage to the central nervous system (CNS) and other organs. EtOH abuse during pregnancy is known to produce teratogenic effects in newborns of virtually all mammalian species. In humans this is termed the "fetal alcohol syndrome" [1]. The CNS is most sensitive to the teratogenic effects of EtOH. It is associated with both morphological and neurochemical abnormalities in the brain, related to the dopaminergic, serotoninergic, cholinergic and other neurotransmitter systems [7, 20, 46].

EtOH administered together with other drugs or chemicals that act mainly on the CNS mostly increased their toxicity. In contrast, in our previous study we found that joint administration of EtOH and cadmium to pregnant rats diminished some neurotoxic effects of the metal and prevented its deposition in the brain of offspring [8, 22, 44].

The aim of this study, therefore, was to investigate the effect of two different Al concentrations administered during pregnancy to rats with or without EtOH on the central dopamine (DA), serotonin (5-HT) and muscarine (M) receptor reactivity in the offspring. In this study we used behavioural procedures (oral activity, yawning, catalepsy) to determine the reactivity of the above mentioned-receptors to specific agonists (SKF 38393, quinpirole, mCPP and pilocarpine) and an antagonist (haloperidol).

Materials and Methods

Experiments were conducted on virgin female Wistar rats weighing about 220 g, and their male offspring. Animals were housed at 22 ±2°C on a 12 hr light: 12 hr dark cycle (from 7:00 am.). Half the female rats were given a 10% solution (v/v) of EtOH in double-distilled water ad libitum along with a standard laboratory diet [40]. The remaining animals (controls), were given double-distilled water only. On the 11 th to 15th days all the female rats were group - housed with male rats at a ratio of 3 females to 1 male. At the same time the rats receiving EtOH or water were divided into 3 subgroups and aluminium sulphate ($Al_2(SO_4)_3 \cdot 18H_20$ - POCH, Poland; 600 or 3000 ppm) was added to the drinking solution of these groups [13]. Control groups were treated with double-distilled water or 10% aqueous solution of EtOH acidified to pH 4.1-4.3 [12]. On the 15th day pregnant rats were housed singly. The volume of fluid consumption was monitored daily for each dam. Al and EtOH were then discontinued and all animals were given double-distilled water. The offspring remained with the dams for 21 days after birth. Behavioural examinations were performed on male offspring about 3 months old.

Testing of Quinpirole - Induced Yawning Activity [31]

For each test session, the rats were placed in individual glass cages in a quiet, well ventillated and well-lit room. Rats were acclimatized to this environment for at least 30 min. Afterwords, each rat was given an i.p. injection of physiological saline (0.9% NaCl; 1 ml/kg) and observed for 60 min for the number of yawns. At the end of this session each rat was injected i.p. with a low dose of quinpirole•HCl* (trans-4aR-4,4a,5,6,7,8a,9 octahydro-5-propyl-1H-pyrazolo (3,4-g) quinoline hydrochloride; 0.0125 mg/kg) and observed for another 60 min. Four rats from different groups were observed simultaneously. The same rats were challenged on subsequent days with increasing doses of quinpirole• HCl (0.025 to 0.2 mg/kg i.p.) and observed in the same way, with only one session per day. Quinpirole is a relatively selective DA D_2/D_3 receptor agonist which in low doses is associated with selective induction of yawning activity in rats [32, 49].

*Quinpirole, SKF 38393 and mCPP were obtained from Research Biochemicals, Inc. (Natic, MA, USA). Pilocarpine and haloperidol was obtain from POLFA (Poland). All doses refer to the salt from.

Testing of SKF 38393, mCPP and Pilocarpine Oral Activity [10, 30]

For each test session rats were acclimatized to the cages as above. Afterwards, the rats were given i.p. injections of SKF 38393 •HCl* (1-phenyl-2,3,4,5-tetrahydro- (1H)-3-benzazepine-7,8-diol hydrochloride; 0.3 to 1.0 mg/kg), mCPP* (1-(3- chlorphenyl) piperazine; 0.3 to 10.0 mg/kg), pilocarpine HCl* (0.1 to 3.0 mg/kg) or the saline vehicle (0.9% NaCl; 1 ml/kg i.p.). Each rat was then observed singly, for 1 min every 10 min, over a 60 min period, beginning 10 min after any of the challenge treatments. Then numbers of spontaneous vacuous chewing movements were counted.

SKF 38393 is a relatively selective central DA D_1 receptor agonist [38], mCPP is a 5-HT_{2C} agonist [24] and pilocarpine a muscarinie (M) agonist [30]. All of them induced oral activity in rats in the range of administered doses [10].

Testing of Haloperidol Catalepsy

Haloperidol* 0.5 mg/kg was administered s.c. and catalepsy was evaluated every 30 min for 150 minutes and presented in scores.

Statistical Analysis

Data from each behavioural study are presented as dose-effect curves. An analysis of variance (ANOVA) and the post - ANOVA test of Newman- Keuls were used to test for statistically significant differences between the group. A P value of 0.05 or less was considered to indicate significance.

Results

The average fluid consumption for pregnant dams receiving EtOH (with or without Al) ranged from 7.7 to 11.0 ml/100 g body mass per day (Tab. 1). In rats receiving water (with or without Al), fluid consumption ranged from 7.1 to 14.0 ml/100 g/day.

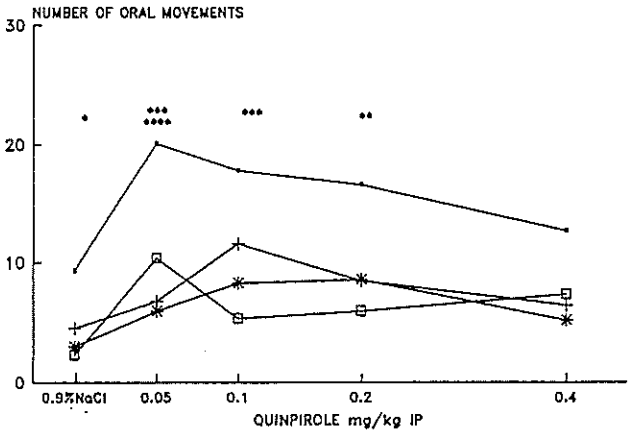
After acute administration of a saline vehicle there was a mean of about 1-2 yawns in each group of rats during the 1 hour observation period. Quinpirole 0.05 mg/kg i.p. produced a maximal response of approximately 25 to 30 yawns in controls, Al 600 and 3000 ppm pretreated groups of rats, apart from rats exposed to 10% EtOH. In that group the maximal yawning response was about 10 yawns. In the offspring exposed during the prenatal period to both concentrations of Al together with EtOH the maximal yawning response was similar to that observed in the EtOH-pretreated rats: 10-15 yawns (results not presented in figures).

Table 1. Mean fluid consumption by pregnant rats given water to which Al (600 or 3000 ppm) or EtOH (10% v/v) had been added.

Group No	Noubers of animals	Fluid consumption (ml/100g of body mass/day)
1. Water	8	14.1±0.8
2. + Al 600 ppm	18	10.4±0.4
3. + Al 3000 ppm	18	7.1±0.3
4. 10% EtOH v/v	30	11.0±0.6
5. + Al 600 ppm	8	9.1±0.6
6. + Al 3000 ppm	15	7.7±0.3

Oral activity of rats following acute administration of physiological saline was about 2-9 oral movements during the observation period in all examined groups. Quinpirole 0.05 mg/kg i.p. increased the oral activity in the control group with a maximal response of 21 oral movements occuring during the observation period (Fig.1). In the other groups of rats examined (EtOH and Al 3000 ppm) response to quinpirole was reduced in a statistically significant manner. Similar results were observed in the rats exposured prenatally to Al 600 ppm and EtOH (results not presented).

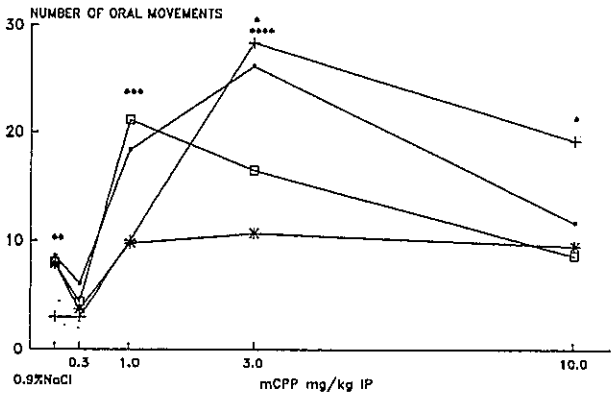
SKF 38393 0.1 mg/kg i.p. increased the oral activity in the control group with a maximal response of about 10 oral movements occuring during the observation period.



Curve 1. — • — Control
Curve 2. — — EtOH 10% v/v
Curve 3. — * — Al 3000 ppm
Curve 4. — + — EtOH 10% v/v + Al 3000 ppm

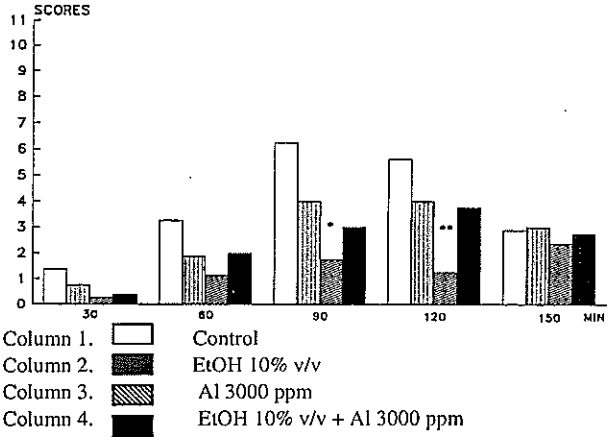
Comparison between curves: 1/3: *2p <0.05; 1/2: **2p <0.025; 1/2 and 1/3: ***2 p <0.02; 1/3: ****2 P <0.01.

Fig. 1. Quinpirole-induced oral activity in male rats exposed to EtOH and/or Al during prenatal development. Pregnant rats received acidified double-distilled water alone (control) or with added EtOH (10% v/v) and/or Al (3000 ppm). At about 3 months after birth, offspring were challenged with saline and then increasing doses of quinpirole •HCl (0.05 to 0.4 mg/kg i.p.). Then the number of oral movements was counted for 1 min every 10 min during the following hour. Each group consisted of 9 rats.



Comparison between curves: 2/2: *2p <0.05; 1/2: **2p <0.02; 2/4: ***2 p <0.01; 1/3: ****2 P <0.001.

Fig. 2. mCPP-induced oral activity in male rats exposed to EtOH and/or Al during prenatal development. Pregnant rats received acidified double-distilled water alone (control) or with added EtOH (10% v/v) and/or Al (3000 ppm). At about 3 months after birth, offspring were challenged with saline and then with increasing doses of mCPP (0.3 to 10.0 mg/kg i.p.). Then the number of oral movements was counted for 1 mm every 10 min during the following hour. Each group consisted of 9 rats. Explanation as in Fig. 1.



Comparison between columns: 1/3 : *2p <0.02; 1/3: **2p <0.01; 3/4: +2 p <0.05.

Fig. 3. Haloperidol 0.5 mg/kg s.c. induced catalepsy in male rats exposed to EtOH (10% v/v and/or Al (3000 ppm) during prenatal development. Each group consisted of 8 rats.

Oral activity was not significantly altered in all the groups examined after challenge with SKF 38393 0.03 to 1.0 mg/kg i.p. (results not presented).

Pilocarpine in the dose range from 1.0 to 3.0 mg/kg increased oral activity from about 10 to 40 oral movements in the control group, respectively. The number of oral movements after pilocarpine 1.0 and 3.0 mg/kg i.p. was lower than that of the control group only in the animals treated with Al 3000 ppm and Al 3000 ppm plus EtOH (results not presented).

A challenge dose of 3.0 mg/kg i.p. of mCPP produced an increase in oral activity in the control group of rats offspring, with maximal response of about 29 oral movements (Fig. 2). The maximal response to mCPP was significantly reduced in rats that were exposed prenatally to EtOH and Al 3000 ppm. In animals treated prenatally jointly with Al 3000 ppm and EtOH, mCPP challenge doses of 3.0 and 10.0 mg/kg i.p. the effects were similar to those in the control group (Fig. 2). Similar results were observed in animals exposed prenatally to Al 600 ppm (results not presented).

Haloperidol 0.5 mg/kg s.c. produced catalepsy in the control animals with maximum 90-120 minutes after its administration (about 7 scores). The intensity of catalepsy in animals exposed prenatally to Al 3000 ppm with or without EtOH was similar to that of the control rats (Fig. 3). In animals exposed during intrauter development to EtOH the intensity of catalepsy after haloperidol 90 and 120 min. observation was significantly decreased in comparison to control rats. Similar but less intense effects were observed in animals exposed prenatally to Al 600 ppm (results not presented).

Discussion

There are numerous reports demonstrating the teratogenic effect of EtOH on the developing nervous system and other tissues of mammals. In addition to its production of gross structural abnormalities, EtOH produces persistent alteration in functional components of identified neurotransmitter systems. These relate to altered synthesis, release, turnover, uptake or level of neurotransmitters in specific brain regions [5, 6,19]. In recent years, greater alteration has been paid to the receptor binding site for neurotransmitters, since downstream neuronal messages and behavioural expressions are dependent on transduction and cellular processing of receptor-messenger coupling. In the present paper we have focused on these processes by observing behaviour-specific actions of agonists and antagonists that are selective for DA and agonists selective for 5-HT and M receptors. In addition, we have examined the combined administration of EtOH and Al during intrauter development modified or influenced reactivity of the above-mentioned central receptors after agonist or antagonist challenge.

In the present study we confirm our previous finding that prenatal EtOH exposure diminished reactivity of the central DA D_2, D_3, 5-HT_{2C}, but not DA D_1 and M receptor reactivity to specific agonists in rat offspring [7, 9]. These observations are in accordance with the finding of others who reported a deficit of striatal D_2 receptors in 63 day-old rat offspring that consumed EtOH in drinking water during pregnancy [33]. Long-term exposure of adult rats for four and half months to Al 600 and 3000 ppm p.o. diminished reactivity of the central DA, 5-HT_{2C} and M receptors and decreased the level of DA and DOPAC in the striatum of rats [42,45]. On the other

hand, Al unlike other heavy metals (such as cadmium or lead), seems to be less toxic to embryos during intrauter development and to have a very weak influence on the central nervous system of mammals. This may be because of the short period of exposure or minimal transfer of Al via the placenta to fetus body. The content of Al in the 20-day-old rat fetuses did not differ significantly in the Al-treated animals (400 mg/kg/day p.o.) from the control group [39]. Others have found cumulation of Al in the placenta of pregnant mice exposed to this metal [12]. In addition, there is some suggestion that young organisms are less sensitive to the toxic actions of Al than adults [43]. We have partially confirmed the above data. Al administered during pregnancy did not affect central DA D_1 and D_3 receptor reactivity in adult rat offspring [42], but it influenced (mainly at higher concentrations) the central DA D_2, 5-HT and M receptor systems [45].

We have previously shown that lead administration during rat pregnancy caused changes in reactivity of the central DA receptors to agonist in the offspring [11]. In another experiment we showed that joint administration of EtOH with cadmium during pregnancy diminishes the neurotoxicity of this metal and prevents its deposits in the brain of offspring [8]. In current literature only Flora et al. [23] found that the effects of Al on biogenic amine changes in the brain or on hematological and hepatic disorders are potentiated by EtOH. Others have shown that EtOH attenuates the neurotoxic effect of Al because of an increased permeability of the intestinal mucosa to the entry of Al and its deposition in the brain [18].

Our results confirm previous findings that EtOH administered during pregnancy decreased reactivity of the central DA D_2, D_3 and 5-HT_{2C} receptors in offspring. EtOH does not modify the effect of Al on reactivity of the central DA D_1, D_2, D_3 and M, but prevents the depressive effect of Al on central 5-HT_{2C} receptor. We cannot explain this last phenomenon.

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