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Changes in Auditory Brainstem Responses in Alpha-linolenic Acid Deficiency as a Function of Age in Rats

Abstract

Auditory brainstem responses (ABRs) to click stimuli have been compared in young (21-day-old), adult (6-month-old), and old (18-month-old) rats fed a normal (Arachid-Colza) or an alpha-linolenic acid deficient (Arachid only) diet. Wave I amplitude and latency did not show any significant change with either age or diet. However, wave III showed a progressive decrease in amplitude and latency from young to adult and from adult to old rats having a normal diet. With alpha-linolenic acid deficiency, wave III amplitude and latency values decreased faster than in the normal diet control groups. Although final values in the old groups with the two diets were similar, with alpha-linolenic acid deficiency values for wave III decreased to this final level in the adult group. These data indicate that the central auditory nervous system ages faster, or earlier, with a fatty acid deficiency.

Key Words

Auditory brainstem responses
Ageing
Diet
Alpha-linolenic-acid
Rats

Introduction

Fatty acids control the structure and function of biological membranes, including those from nervous tissue. Some of these fatty acids are polyunsaturated, and are derived from the dietary precursors linoleic and alpha-linolenic acid.

The essential nature of alpha-linolenic acid is beyond doubt. A deficiency leads to anomalies in the composition of nervous membranes in various species,[1–11] and in their architecture and function. This leads to perturbation of both neurotransmitter levels[12] and electrophysiological parameters, as indicated by the electroretinogram, and to alteration in learning abilities, and greater sensitivity to neurotoxins.[2,13–20]

Nutritional deficiency in $(n-3)$ fatty acids alters the brain structure and function in humans as previously demonstrated in animals. The biochemical correlation between dietary fatty acids, milk composition and, possibly, brain composition has been demonstrated in humans,[21–24] as very long polyunsaturated chains are present in human milk and because of the vast amount of these fatty acids deposited in nervous tissue during the perinatal period. Retinal and visual cortex electrophysiology, and intellectual functions are improved in babies fed a diet enrichedin $(n-3)$ fatty acids.[25,26] Some neurological differences have been found between nine-year-old children fed breast milk or formula milk as babies. It is suggested that very long poly-unsaturated fatty acids may explain this discrepancy.[27]

As dietary alpha-linolenic acid clearly controls some electrophysiological measures, such as the electroretinogram in various species including monkey and human,[1,21,28–32] this work was designed to determine whether auditory evoked potentials are also affected.

In order to study the peripheral and central changes associated with the different diets and as a function of age, eighth nerve and auditory brainstem responses (ABRs) were recorded and measured in the rat. These responses present as a sequence of five waves of roughly 0.6 ms intervals (Figure 1). Waves I and III were particularly studied because they are the most prominent waves in rat[33] and their amplitude and latency are the best indicators of peripheral and central auditory function, respectively.[34]

Materials and Methods

Animals

Female Wistar rats originating from Iffa Credo (l'Arbresle, France) and bred in the laboratory were divided into two groups. The two groups were fed the same diet, except for lipids at least 15 days before breeding. The total amount of lipid was 6 per cent in each diet. In the group fed an alpha-linolenic acid deficient diet, the lipids were peanut oil containing 1200 mg of linoleic acid per 100 g diet (18:2$(n-6)$) (Arachid (A) Group). In the group fed the control diet, non-deficient in alpha-linolenic acid, the fat used was a mixture of peanut oil and rape seed oil containing 1200 mg linoleic acid and 200 mg alpha-linolenic acid per 100 g diet (Arachid-Colza (AC) Group). Diets were given ad libitum. The quality of oils was carefully examined with

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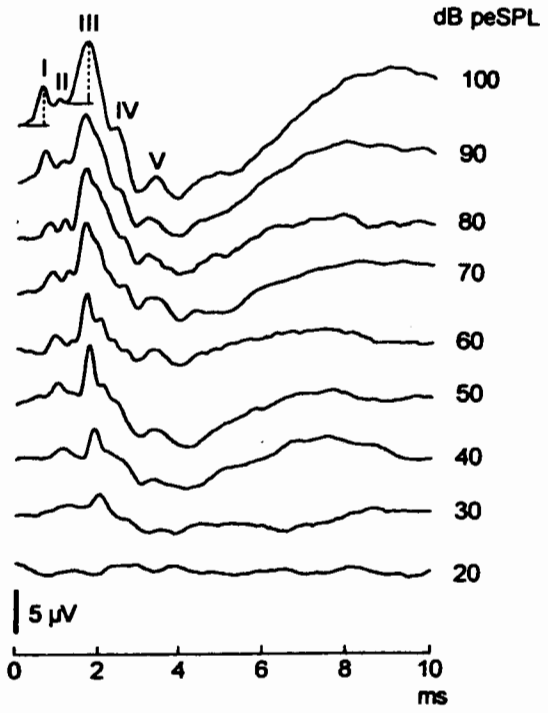

Figure 1. Typical recordings of auditory brainstem responses (ABRs) in a normal adult rat in response to clicks of different intensity levels. On the upper trace at 100 dB peSPL, the successive peaks (I to V) are indicated. Latencies of peaks I and III are measured from onset of click stimulus at the ear drum (time 0). Amplitudes are measured as indicated (vertex positive up).

regard to fatty acids and antioxidants. The toxicological analysis (performed by the Institut National de la Recherche Agronomique, Dijon, France) showed there to be no contaminants and no detectable level of oxidized fatty acids or of 'trans' structures. The diets were prepared by the Institut National de la Recherche Agronomique (INRA-CNRS), 78350 Jouy-en-Josas, France. Breeding and experimental rooms were thermostatically maintained at 21±1°C. The offspring from these two groups were maintained respectively on the same AC or A diets and divided into three subgroups of young (y) 21-day-old rats, adult (a) 6-month-old, and old (o) 18-month-old rats. The number of animals from which data were actually obtained is shown in Table 1 relative to the total initial number of animals in each group. Some animals, particularly in the older groups, died before measurements were taken or were eliminated due to the presence of otitis media, which was systematically checked.

Experimental protocols were approved and met government guidelines (Ministry of Agriculture, authorization No. 03007, June 4, 1991).

Electrophysiology

The rats were anaesthetized with an intramuscular injection of 1 ml/kg body weight of a mixture of two volumes of ketamine chlorhydrate (Ketalar, Parke Davis, 50 mg/ml) and one volume of 2 per cent xylazine (Rompun, Bayer). Stainless steel needle electrodes were pushed under the skin at the vertex, left (ipsilateral) mastoid and neck (ground electrode). Signals between the vertex and mastoid were amplified in a laboratory-made amplifier (×20,000, 100–3,000 Hz) and averaged in a computer-controlled signal averager system (CED 1401plus Cambridge Electronic Design, Cambridge, UK). Click and tone-pip acoustical stimuli were generated in a PC controlled signal generating board (0.1 ms pulses of alternate polarity for click generation, gaussian shaped envelopes of 4 ms duration for tone pips at octave frequencies from 1 to 32 kHz), amplified and sent to a headphone (Sennheiser, HD 480 II) placed 2 cm lateral to the tested (left) ear. Stimuli were presented at the rate of 10 per second; 100 to 1,000 responses were averaged. Thresholds of responses were determined for wave III, which is the most prominent wave at low levels of stimulation, at the different tone-pip frequencies (ABR audiograms), and responses to the click from threshold to 80 dB peSPL were recorded in 10 dB increments. Amplitude and latency were measured for waves I and III (Figure 1), and the input/output functions were analysed. Statistical differences were evaluated between each condition pair on input–output amplitude and latency functions using two-way ANOVA.

Results

The weight of the animals changed with age, from 60 ± 5 g at 21 days to 434 ± 23 g at 6 months and 508 ± 50 g at 18 months in the control (AC) groups. There was no significant difference in weight between this control (AC) group and the experimental (A) group.

Audiograms

All rats in all the groups except the control old group (ACo) gave ABR audiograms within normal limits. In group ACo, two animals had a normal audiogram and four showed slight threshold elevations at the highest frequencies, which resulted in a non-significant overall mean high frequency threshold elevation (Figure 2).

Input–Output Amplitude and Latency Functions

There was no significant difference in wave I amplitude and latency with age in either group at any intensity, whereas the later waves showed consistent changes (Figures 3 and 4).

Table 1

Diet	*Young*	*Adult*	*Old*
Arachid + colza	ACy = 10/10	ACa = 6/8	ACo = 6/8
Arachid	Ay = 9/10	Aa = 6/9	Ao = 4/7

Final/initial numbers of animals in each group. (A=arachid, C=colza, y=young, a=adult, o=old).

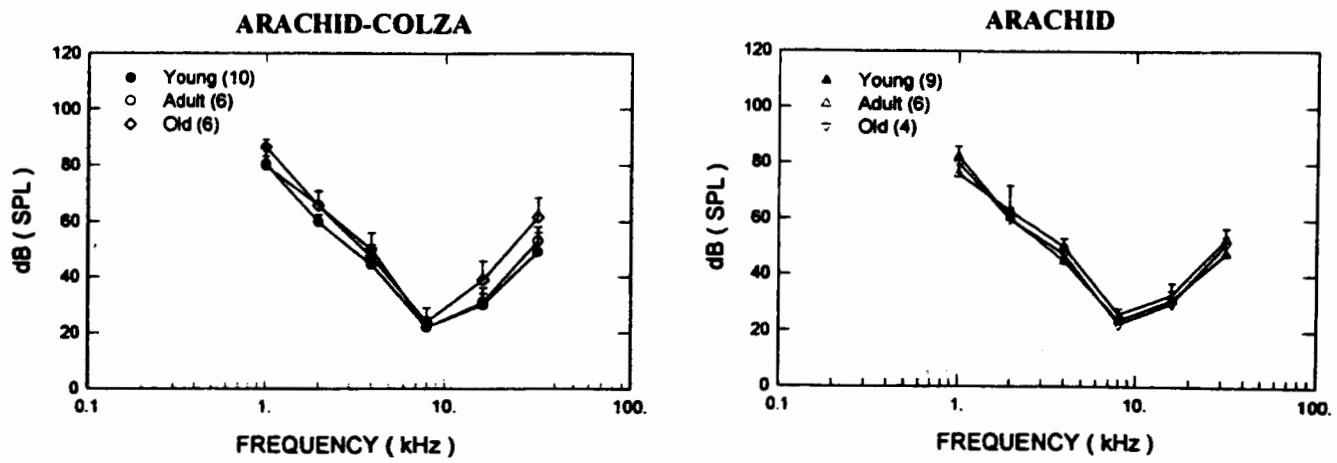

Figure 2. Wave III threshold intensity as a function of frequency (ABR audiograms) in young, adult and old control rats (normal arachid-colza diet, left) and in alpha-linolenic acid deficient rats (arachid alone diet, right).

There was a significant difference in wave III amplitude in the young rats between the two diets (ACy and Ay, $p<0.05$). All the other differences were highly significant ($p< 0.001$).

In both the control (AC) and the experimental (A) groups, wave III showed a progressive decrease in amplitude and in latency with increase in age. The values for adult rats were between the young and old values (Figures 3 and 4).

The amplitudes in the control adult group (ACa) were significantly different from those in the young (ACy and Ay) and in the old (ACo and Ao) groups (Table 2). In the experimental group, the amplitude values for adult rats (Aa) were statistically different from the values in the young rats (ACy and Ay) but similar to those in the old rats (ACo and Ao). Amplitude values in the old groups were similar.

The decrease in wave III latency, compared with the unchanged latency of wave I (Figure 4), resulted in a shortening of the I-III intervals. Here, also, changes were similar from young to old rats in the two groups. Wave III latencies in all old groups were different from those in the young groups (Table 2). Wave III latency values in the control adult group (ACa) appear somehow in between the values in the young and old groups (Figure 4, left), while in the experimental group (Aa) they were more similar to those of the old group (Ao) (Figure 4, right). However, the differences were not significant (Table 2).

Discussion

Maturation of the cochlea and eighth nerve is achieved in the rat at post-natal day 16; however, the central nervous system matures over a longer period. Thus at the 21st day the auditory periphery in rats, but not the CNS, is mature. At six months the rats are young adults while at 18 months they can be considered as old, although at an early stage, since ageing in the rat can extend up to more than 33 months.

Since the threshold audiograms, and the amplitudes and latencies of the scalp recorded click evoked eighth nerve compound action potentials (wave I) as a function of click level, do not change significantly with age, it appears that normal ageing had no effect on the peripheral auditory function. Most of the studies dealing with ageing and ABRs have described an increase in wave I latency which is due to peripheral 'presbyacusis', a progressive high-frequency hearing loss which develops in man (as in most mammals) with age and which corresponds to an alteration of the sensorineural structures particularly at the base of the cochlea (which is most sensitive to any adverse condition such as acoustical overstimulation, metabolic disorders or ototoxic drug treatments). This basal impairment introduces a travelling wave delay from the oval window to the remote site of activation on the basilar membrane of the remaining functional sensori-neural structures. Although we did not monitor thresholds at the highest frequencies (above 32 kHz), the fact that wave I latency does not increase with age, whatever the level of click stimulation, typically indicates that the base of the cochlea is not affected. Only the slight high-frequency threshold elevations in the old control group would indicate potential development of peripheral 'presbyacusis'. The results of the present study in normal ageing rats are in agreement with those of Crowley et al.[35,36] who have shown that both cochlear electrophysiological responses and hair cell counts vary little in rats until 18 months. Only very old rats show significant cochlear changes. Keithley and Feldman[37,38] also showed significant hair cell and spiral ganglion cell losses only at and after 23 months. These changes with ageing are far less pronounced than in man.[39,40]

However, changes with age develop in the later wave III which, assuming that there are no changes at the periphery, would reflect changes in the central auditory nervous system (CANS). In the control group (AC), the very significant changes from young to adult rats could be related to maturation in the central nervous system.[41] The shortening in latencies particularly could correspond to an increased velocity of influx associated with myelination of the fibres. However, the decrease in amplitude does not fit with such a decrease in latency which should be in support of a better synchrony of activities and thus of a larger amplitude of the responses. Since such a decrease in amplitude and in latency continues with age, we should consider, however, that they are related to normal ageing, although at this point it is difficult to determine whether such changes are due to typical neural deterioration or to other physical and morphological changes affecting the far-field electrical conditions of recording the responses from the remote central auditory structures (head size, body weight, temperature, etc.).

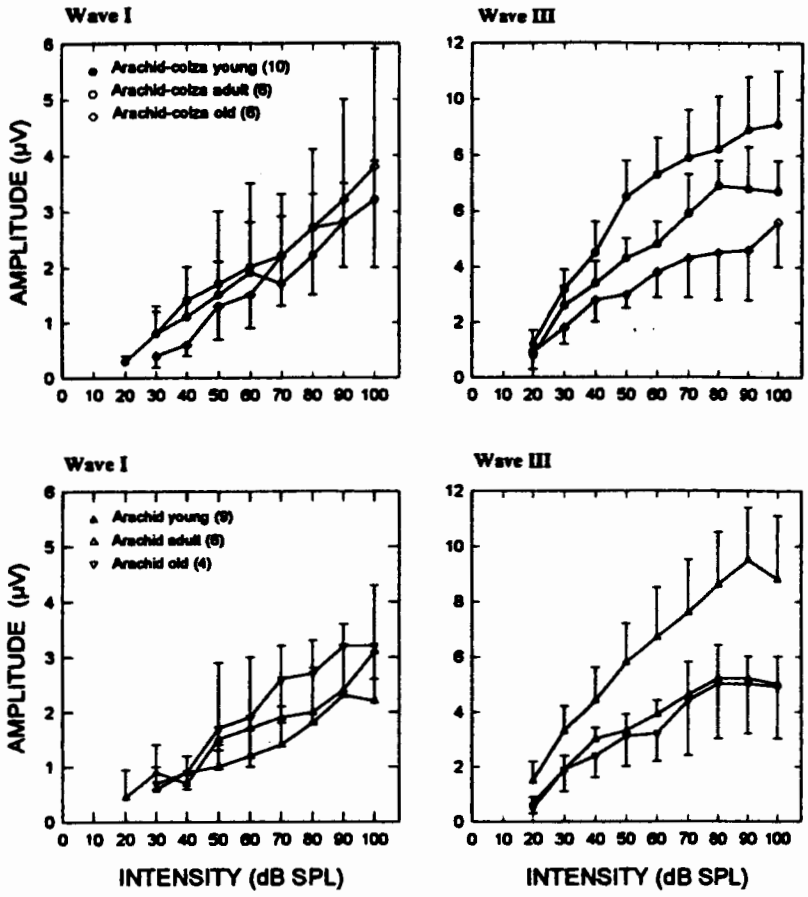

Figure 3. Mean amplitudes (± sd) of waves I and III as a function of click intensity in the young, adult and old rats in the two groups with normal (arachid-colza, top) and alpha-linolenic-acid deficient (arachid, bottom) diets respectively.

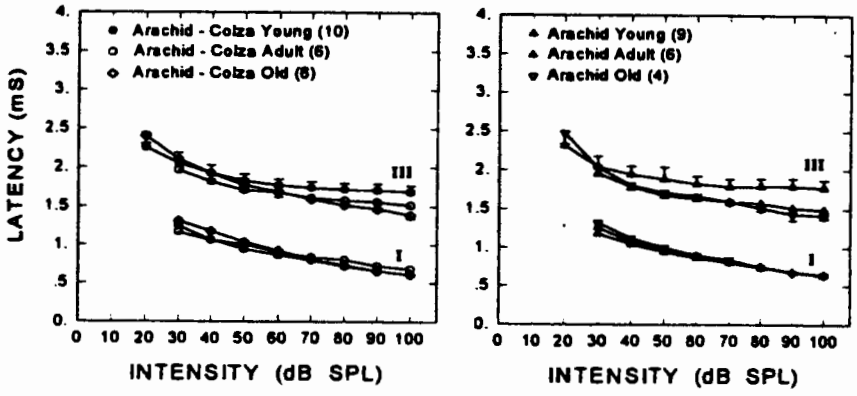

Figure 4. Mean latencies (± sd) of waves I and III as a function of click intensity in the young, adult and old rats in the two groups with normal (arachid-colza, left) and alpha-linolenic-acid deficient (arachid, right) diets respectively.

The present data from the normal control rats confirm many other studies in various species which do not show any significant change in the latency of ABR waves as long as there is no significant hearing loss.[42] A more recent study in humans describes an increase in wave I latency but no changes in the latencies of waves II and III, and thus rather a shortening of the I–II and I–III intervals.[43] Also, single unit studies in old Sprague–Dawley rats' lateral superior olive (LSO) did not show any increase in conduction time.[44] In our study, not only do we not observe an increase in wave I latency, but we observe a

Table 2. Two-way ANOVA analyses of amplitude and latency functions (respectively above and below the diagonal of the table) in the different groups.

	Amplitudes					
	ACy	*Ay*	*ACa*	*Aa*	*ACo*	*Ao*
ACy			***	***	***	***
Ay	*		***	***	***	***
ACa	***	***		***	***	***
Aa	***	***				
ACo	***	***				
Ao	***	***				
	Latencies					

*: $p<0.05$ ***: $p<0.0001$

decrease in wave III latency with age, so that the end result is the same as that reported by Costa et al.,[43] i.e. decreased I–III intervals.

However, the study of Finlayson and Caspary[44] has also shown that LSO single unit responses in Sprague–Dawley rats do not change, either in latency or in discharge rate levels. Thus if the decreased amplitude of ABR waves is related to neural impairment, that should correspond to a decrease in the number of activated neurones, due either to a neuronal loss[38] or to a decrease in the number of synaptic terminals.[45]

Amplitude of the brainstem responses and their change with age have rarely been studied, due to the high variability of the amplitude measurements, compared to the accuracy of latency measurements.[40] However, Beagley and Sheldrake[46] have shown in humans that latencies do not change with age but amplitudes decrease significantly. Psatta and Matei[47] have presented normative values of ABRs amplitudes from 1 to 70 years of age in normally hearing subjects. They found highly significant changes in amplitudes as a function of age: they describe an increase in amplitude from 1 to 10 years of age, for all waves except wave I, followed by a decrease of amplitude from 10 to 70 years, with a slower rate from 50 to 70 years. Our observation of a significant decrease of wave III amplitude with age in rats is in good agreement with this human data.

The differences between the control (AC) group and the experimental (A) group are in the amplitude values of young and adult rats. This difference is small in the young groups (ACy and Ay). However, the alpha-linolenic acid deficient adult rats (Aa) have amplitudes similar to the old rats of either group (Ao and ACo), while the control adult group (ACa) differs from these two old groups. Although in these experiments latency changes with age between control and experimental groups are not significantly different, there is a tendency similar to that observed for the amplitudes. The small number of animals, and the relative small changes of latency with age, compared to those of the amplitude, do not exclude the possibility of a similar effect for both amplitude and latency. It must be noted that these two adult control and experimental groups were evaluated blindly at the same time, had the same origin and the same weight so that the actual difference was only the diet. Thus, on the basis of amplitudes of the central component of the auditory brainstem responses, it appears that the central auditory nervous system of the alpha-linolenic acid deficient rats aged faster, or earlier, than that of the normal control rats.

Early postnatal undernutrition delays the development of ABRs in rats, and nutritional rehabilitation can make the groups 'catch up' on ABRs,[48] as with thiamine-deficient diets.[49] Maturation is also delayed and wave I latency and central conduction time are increased in kittens from mothers fed a taurine-deficient diet.[50] Dietary zinc deficiency has no effect on auditory brainstem responses in the rat.[50] High dietary sulphur impairs brainstem functions and ABRs.[52] Alcohol-addicted 22-month-old rats do not show any significant threshold changes as compared with either normal 22-month-old or 3-month-old rats, while the 22-month-old normal rats show a high-frequency hearing loss compared with those 3 months old.[53]

Biochemical analyses remain to be performed on the nervous structures involved in audition under these different nutritional conditions. We have previously shown for some tissues that, when the dietary content of alpha-linolenic acid is increased, the level of docosahexaenoic acid (DHA) increases linearly until the alpha-linolenic acid level reaches 200 mg/100 g diet. Above this level in cerebral structures, excess dietary alpha-linolenic acid does not lead to an increase in DHA in tissues. In contrast, in other tissues, there is a slight increase in DHA content.[54] Thus, this DHA concentration should also be evaluated in the cochlea and the eighth nerve of normal and alpha-linolenic acid-deficient rats.

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