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Phenytoin ameliorates the memory deficit induced in the young chick by ethanol toxicity in association with thiamine deficiency

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Abstract

The experiments reported in this series of studies demonstrate that thiamine deficiency, induced pharmacologically by oxythiamine (OT) coupled with the acute administration of ethanol can adversely affect memory processing in the young chick. The interaction between the avitaminosis and ethanol neurotoxicity exerted its effects through the inhibition of the development of the intermediate (ITM) stage of memory (i.e., following 10 min after training), consequently affecting development of the long-term stage of memory and leaving the short-term memory stage intact. The amnesic effect of OT-induced thiamine deficiency and exposure to alcohol was ameliorated by the administration of phenytoin [diphenylhydantoin (DPH)] immediately following the training experience. As the ITM stage of memory has been suggested to rely on the activities of Na^+/K^+ ATPase, and as DPH is a facilitator of Na^+/K^+ ATPase activity amongst its other actions, it may be that the combined effect of OT and ethanol exposure is by interfering with Na^+/K^+ ATPase activity, thus undermining the expression and maintenance of the memory in the period from 10 min following aversant training.

Keywords: Thiamine; Memory; Wernicke–Korsakoff syndrome; Oxythiamine; Pyrithiamine; Ethanol; Day-old chick

1. Introduction

Three recent studies conducted in our laboratories (Crowe and Kempton, 1997; McLaren et al., 1993; Stojanovska, 1993) have shown that thiamine deficiency has a deleterious effect upon memory function in the young chick. The first study (McLaren et al., 1993) demonstrated that when chicks were pretreated with pyrithiamine (PT) and then trained on the passive avoidance learning (PAL) task, the pretreatment produced both anterograde and retrograde memory loss for the training task with memory impairment occurring between 5 and 25 min after learning. This memory loss was associated with a profound disruption of levels of thiamine activity as assessed by erythrocyte transketolase activity in the chicks [non-PT-treated: $M = 282.7$ mU/g Hb, S.D. = 31.9; PT-treated: $M = 114.8$ mU/g Hb, S.D. = 35.4; $t(14) = 13.71$, $P < .0001$].

A second series of studies conducted by Stojanovska (1993) undertook a more extensive analysis of thiamine deficiency in the young chick using oxythiamine (OT). While previous studies using rat models of the Wernicke–Korsakoff syndrome (e.g., Langlais, 1995a,b; Langlais and Mair, 1990; Mair and McEntee, 1983; Mair et al., 1991a,b) have used PT to induce thiamine deficiency, this series of studies established that equivalent memory deficits to those produced by PT could be induced in the young chick using OT. This similarity of effect was thought to be because of the rudimentary quality of the blood–brain barrier in the neonate chick that allowed OT to penetrate the barrier, causing the memory deficits and ataxia. Stojanovska (1993), using OT to induce thiamine deficiency, demonstrated that chicks trained on a passive avoidance task (PAT) showed memory loss from 10 min following training.

The study conducted by Crowe and Kempton (1997) provided the first evidence of an interactive effect between thiamine deficiency and alcohol neurotoxicity in the impairment of memory retention in the young chick. These authors demonstrated that a 2.5-mg dose of OT administered over 2 days yielded memory deficits from 10 min following passive avoidance learning. The memory deficit existed in association with an attenuation of righting reflex. Administration of thiamine (1.0 mg per chick) reversed the memory

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deficit and the slowing of righting reflex. A combination of OT and peripheral alcohol administration also resulted in memory deficits appearing from 10 min after training. However, in contrast to the effect of thiamine deficiency alone, the deficits induced by thiamine deficiency in association with acute administration of alcohol could not be reversed by thiamine resupplementation. The combination of alcohol and OT also slowed the righting reflex. Yet, higher doses of thiamine (i.e., 1.4–3.0 mg per chick) were unable to ameliorate the memory deficit caused by the combination of OT and alcohol. However, the slowing of righting reflex was reversed.

Stojanovska (1993) also demonstrated that the membrane stabilizer, diphenylhydantoin (DPH), was able to counteract the loss of memory in OT-treated chicks. Whilst DPH has been credited with a number of actions on ion channels and synaptic transmission (Rogawski and Porter, 1990), on monoamines, glutamate and GABA activity (Cunningham et al., 2000; Okada et al., 1997) and on folate activity (Carl et al., 1997), it is also a known facilitator of Na^+/K^+ ATPase (e.g., Guillaume et al., 1989; Gutman and Boonyaviroj, 1977; Imaizumi et al., 1995; Lampley et al., 1995; Murakami and Furui, 1994), particularly in situations of cerebral ischaemia.

It has been suggested that the formation of the intermediate term (ITM) stage of memory proposed by the three-stage memory model (Gibbs and Ng, 1977; Ng and Gibbs, 1991) may rely of the action of the Na^+/K^+ ATPase-driven electrogenic sodium pump, producing a state of neuronal hyperpolarization associated with the pump (Gibbs and Ng, 1976, 1977). Both Gibbs and Ng (1977) and Patterson et al. (1986) have demonstrated that intracranial injections of Na^+/K^+ ATPase inhibitors (i.e., ouabain and ethacrynic acid) produce amnesia from 10 min after training and that this amnesia can be overcome by treatment with DPH (Gibbs and Ng, 1976, 1984).

The series of studies undertaken in this investigation aimed to determine whether the deficit in memory in the young chicks induced by thiamine deficiency in association with ethanol neurotoxicity could be overcome by the application of DPH and what stage in the processing of memory that this facilitation affected.

2. General methods

2.1. Animals

Day-old white-Leghorn black-Australorp cockerels were obtained from a local hatchery on the morning of each experiment. Chicks were randomly placed in pairs into open-topped wooden boxes ($20 \times 25 \times 20$ cm), one chick from each pair being marked for identification. Each box was illuminated by a single, white incandescent light bulb (25 W), which in combination with the ducted heating maintained the temperature of the boxes between 25 and 29 °C. Each chick had ad lib access to water at all times, except during the pretraining, training and testing periods on the final day of the experiment.

2.2. Drugs

All drugs used in this series of experiments were administered freehand by subcutaneous injection into a ventral skinfold just below the rib cage. One-milliliter syringes (Becton-Dickinson Tuberculin) fitted with a 27.5-G needle were used for injection of test compounds and vehicle alike. OT (Sigma) and thiamine hydrochloride (TH; Sigma) were each dissolved in 154-mM (0.9%) isotonic saline (NaCl) to the required concentration and were injected in a 100-μl volume per chick. Saline was administered as a control in each experiment. In experiments where ethanol (EtOH; CSR Distillers) was used, it was diluted to 40% in double distilled water and was injected subcutaneously in a volume of 100 μl per chick. All drugs were injected blindly. The codes were not broken until after the retention testing and the measurement of righting reflex had been completed.

2.3. Procedure

The procedure employed was the same for each experiment. Specific modifications made to the general procedure are presented in the descriptions of each individual study.

The learning task employed in the experiments was an adaptation of Cherkin's (1971) passive avoidance task (as modified by Crowe and Hamalainen, 2001; Gibbs and Ng, 1977; Ng and Gibbs, 1991), so that memory was indexed by colour discrimination of the pecking response. Essentially, on Day 3 of each experiment, all chicks were given four pretraining trials, one training trial and one retention trial. In all trials (pretraining, training and retention), the beads were presented to the chicks for a 10-s interval.

In the first two pretraining trials, a chrome bead coated with water was presented to the chick with a view to reinforcing a pecking response. The next two pretraining trials involved a determination of the baseline pecking rates of each chick to a red and a blue bead. After an interval of at least 30 min, a bead similar in type to the red bead used during the latter pretraining trial was covered with the chemical aversant methyl anthranilate. At various training test intervals (TTI) following the training trial, the chicks were presented with an identical red and blue bead to those used during the pretraining trials. The differential level of pecking to the respective beads was used as the dependent variable. The index used to measure retention was the discrimination ratio (DR). The DR is defined as the number (n) of pecks on the blue bead (B) divided by the total number of pecks on the red bead (R) and blue bead:

$$\mathrm{DR} = \frac{n(\mathrm{B})}{n(\mathrm{B})+n(\mathrm{R})}$$

A DR of 1.0 represents perfect discriminated memory and a DR of 0.5 represents no discriminated memory of the aversive vs. nonaversive bead. The DR provides an interval scale measure of retention level and allows interval statistical methods to be applied. Chicks failing to peck at the blue bead on this trial were excluded from later data analysis, on the basis that failure to discriminate between the aversive and the nonaversive beads reflects a generalized avoidance and was therefore not a true index of discriminated memory, rendering the DR for chicks avoiding both beads indeterminate (Ng and Gibbs, 1991). No more than 10% of the birds in each subgroup were rejected on these grounds. The procedure for these experiments has been described in full (Gibbs and Ng, 1977; Ng and Gibbs, 1991).

2.4. Experiment 1: DPH dose–response

Stojanovska (1993) has previously demonstrated that DPH was able to overcome the amnesic effects of OT-induced thiamine deficiency in the young chick. It thus seems reasonable to suppose that the memory-related cellular processes disrupted in thiamine deficiency may be associated with disturbances in the activity of Na^+/K^+ ATPase and would thus be facilitated by DPH, a facilitator of Na^+/K^+ ATPase.

Since interference with activity with Na^+/K^+ ATPase has been implicated in states of thiamine deficiency, the aim of this experiment was to determine whether DPH could effectively counteract OT- and ethanol-induced amnesia. Previous studies have shown that the facilitative effect of DPH is dose dependent (Gibbs and Ng, 1976, 1984; Stojanovska, 1993), with a dose of 10^{-4} M being optimal for counteracting OT-, ouabain- and CXM-induced amnesia (Gibbs and Ng, 1984), while very high (10^{-3} M) or very low (10^{-10} M) doses cause a decrease in Na^+/K^+ ATPase activity. As such, it was of interest to determine the optimal dose of DPH required to overcome the effects of OT-induced amnesia, particularly in chicks that had also been pretreated with ethanol.

In this experiment, a dose–response study using DPH- and saline-treated chicks was undertaken to ascertain whether DPH was capable of facilitating memory functions in chicks rendered thiamine deficient, ethanol neurotoxic or a combination of these states and had had their thiamine deficiency reversed by administration of thiamine.

2.4.1. Method

Chicks ($N=240$) were divided into four equal treatment groups. In the saline/OT treatment group, 60 chicks received a total dose of 2.5-mg OT (dissolved in saline), followed by two injections of 154-mM NaCl, administered in a split doses over 2 days. In the OT/ethanol treatment group, 60 chicks received a total dose of 2.5-mg OT, followed by two injections of 2.72-g/kg EtOH, over 2 days. In the saline/saline treatment group, 60 chicks received two injections of 154-mm NaCl on both Days 1 and 2 of the experiment. Lastly, in the saline/ethanol treatment group, 60 chicks received two injections of 154-mM NaCl, followed by two injections of 2.72-g/kg EtOH, over 2 days.

On Day 3, 1 h prior to initiation of the pretraining phase, each chick was given a subcutaneous injection of 1.0-mg TH and given ad lib access to chick mash. All injections were administered in a 100-μl volume. Chicks were then trained on the one trial passive avoidance task. Immediately after training (i.e., within 10 s of the training), each chick received a subcutaneous injection of either 154-mm NaCl or DPH (i.e., 10^{-4} or 10^{-2} M). All chicks were assessed for their recall of the training experience 180 min after initial training.

2.4.2. Results and discussion

The results of Experiment 1 are presented in Fig. 1. Examination of the Fig. 1 indicates that memory was compromised in subjects pretreated with ethanol and OT, but this effect was ameliorated with a 10^{-4}-M dose of DPH. A two-way (Treatment × Dose) analysis of variance (ANOVA), with unweighted means, revealed a significant treatment main effect [$F_{(3,201)}=14.37$, $P<.001$]. No significant dose main effect was obtained. Furthermore, there was a significant interaction effect between the treatment and dose of DPH administered [$F_{(6,201)}=3.15$, $P<.01$]. Simple main effects analysis showed a significant difference between the four treatment groups for both the saline [$F_{(3,212)}=14.82$, $P<.001$] and the 10^{-2} M dose of DPH [$F_{(3,212)}=5.07$, $P<.01$]. No significant difference was found between the four treatment groups for the 10^{-4}-M DPH dose. Simple main effects analysis revealed that the only significant differences were between the DPH doses for the OT/EtOH-pretreated group [$F_{(2,212)}=9.02$, $P<.001$]. No significant differences were found for the other treatment groups.

The results of Experiment 1 indicate that chicks pretreated with OT and ethanol and given a 10^{-4}-M dose of DPH demonstrate facilitation of memory retention. This effect was not observed in other pretreated groups. Furthermore, in the case of the saline/saline and saline/OT groups, DPH did not, at any dose tested, facilitate memory retention. Additionally, for chicks pretreated with OT and ethanol, DPH facilitated memory retention when given in a dose of 10^{-4} M. This result is consistent with previous findings from our laboratories (Stojanovska, 1993) and with those of Gibbs and Ng (1976, 1984).

2.5. Experiment 2: DPH time course of injection

Research using DPH to counteract the effects of OT-induced amnesia has demonstrated that chicks administered DPH immediately following the learning experience show higher levels of memory retention (Stojanovska, 1993). Furthermore, Gibbs and Ng (1984) have demonstrated that as the interval between the time of learning and the time of injection increases, the counteractive effect of DPH decreases. Hence, in this experiment, a time of injection study using DPH- and saline-treated chicks was undertaken

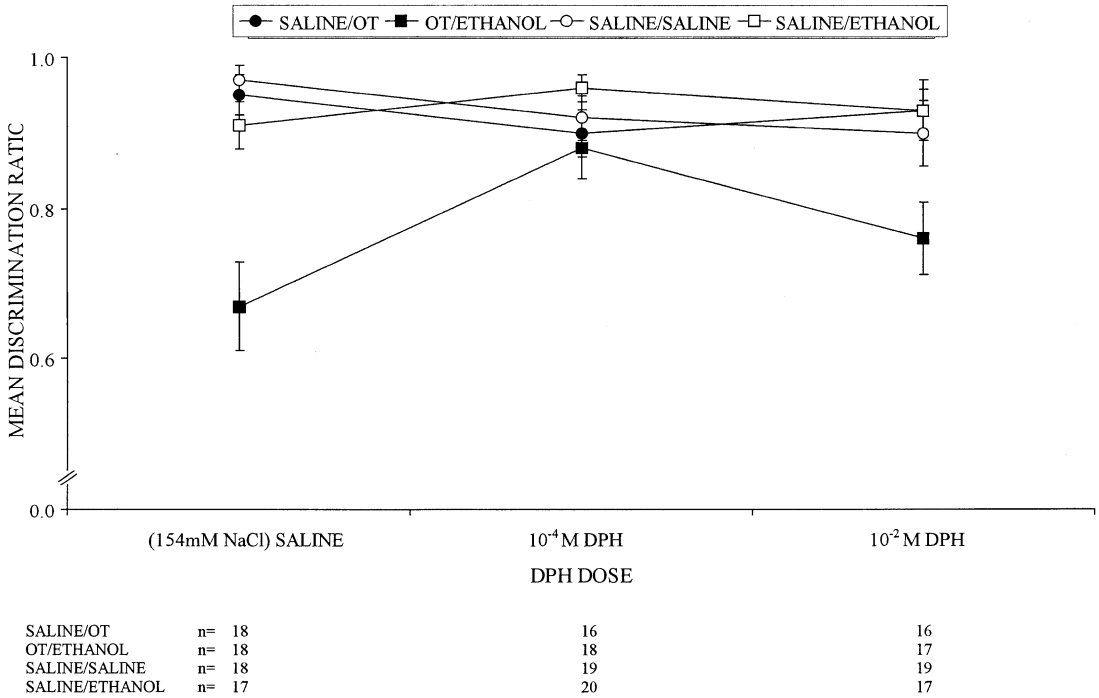

Fig. 1. The effect of various doses of DPH on mean DR (±S.E.M.). Chicks were pretreated with OT, EtOH, NaCl or a combination of these injected 24 and 48 h prior to pretraining. DPH was injected on Day 3, immediately following the learning experience and tested at 180 min following training.

to ascertain the most effective time window of administration of DPH. It was expected that DPH would counteract OT-induced amnesia when administered immediately following the learning experience and that injections administered either prior to, or long after the learning experience, would result in weaker retention of the learning experience.

2.5.1. Methods

Chicks ($N=140$) were divided into three treatment groups. In the OT/ethanol treatment group, 120 chicks received a total dose of 2.5-mg OT (dissolved in saline), followed by two injections of 2.72-g/kg EtOH, over 2 days. In the saline/saline treatment group, 20 chicks received two injections of 154-mM NaCl on both Days 1 and 2 of the experiment. On Day 3, 1 h prior to the initiation of the pretraining phase, each chick was administered an injection of 1.0-mg TH and allowed ad lib access to chick mash. All injections were administered in a 100-μl volume. They were then trained on the passive avoidance task.

A single injection of 10^{-4}-M DPH (15 or 30 min before training or immediately, 15 and 30 min after training) was administered. All chicks were assessed for their recall of the training experience 180 min after initial training.

2.5.2. Results and discussion

The results of Experiment 2 are presented in Fig. 2. A one-way between-groups ANOVA, with unweighted means, revealed that there was no significant difference in memory retention across the different injection times for chicks pretreated with OT and ethanol and then injected with DPH. However, a one-way between-groups ANOVA, with unweighted means, revealed that there was a significant difference in memory retention between groups treated with either DPH or saline immediately following the training experience [$F_{(2,49)}=10.14$, $P<.001$]. Post hoc comparisons, using the Tukey method, revealed that there was a significant difference between the OT/ethanol/DPH group and OT/ethanol/saline group ($P<.01$) and the OT/ethanol/saline group and saline/saline/DPH group ($P<.01$). No significant difference was found between the OT/ethanol/DPH group and saline/saline/DPH group.

The results of Experiment 2 indicate that while there was no significant difference across the five time points, visual inspection of the data for the OT/ethanol/DPH treatment group suggested that the most effective time of administration for DPH was immediately following the training experience. The effectiveness of DPH, in ameliorating the effects of combined thiamine deficiency and ethanol neurotoxicity, immediately following training, was demonstrated by the diminished memory retention seen in chicks that were made thiamine deficient and ethanol neurotoxic but received only a saline injection following learning.

The results of Experiment 2 are consistent with those of Experiment 1 in indicating that a dose of 10^{-4}-M DPH can effectively counteract OT/ethanol-induced amnesia.

2.6. Experiment 3: DPH time course of retention

Previous research in our laboratories (Crowe and Kempton, 1997; McLaren et al., 1993; Stojanovska, 1993) have

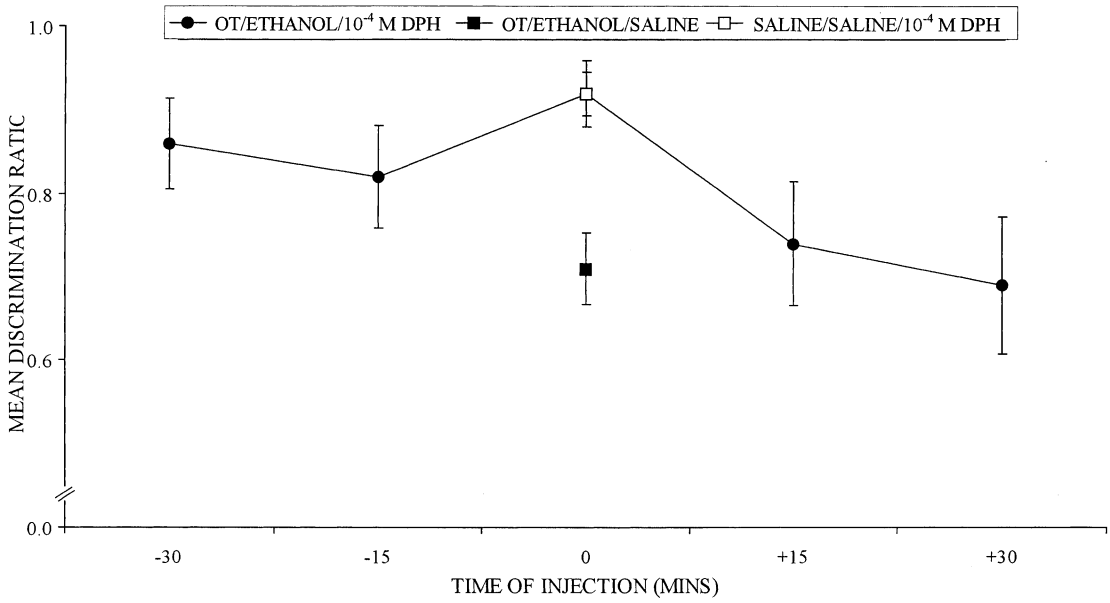

Fig. 2. The effect of 10^{-4}-mM DPH on mean DR (±S.E.M.), when administered at various times before, immediately and after the training experience. Chicks were pretreated with OT and EtOH or NaCl, injected 24 and 48 h prior to pretraining, and treated with either DPH or NaCl. Chicks were tested at 180 min after the training experience.

shown that thiamine plays an important role in the cellular processes that underlie memory formation and that both OT and PT impair the formation of ITM and LTM while leaving the STM stage intact.

In this experiment, a time course of retention function using DPH- and saline-treated chicks was undertaken to ascertain the memory stages that were altered as a consequence of administration of DPH.

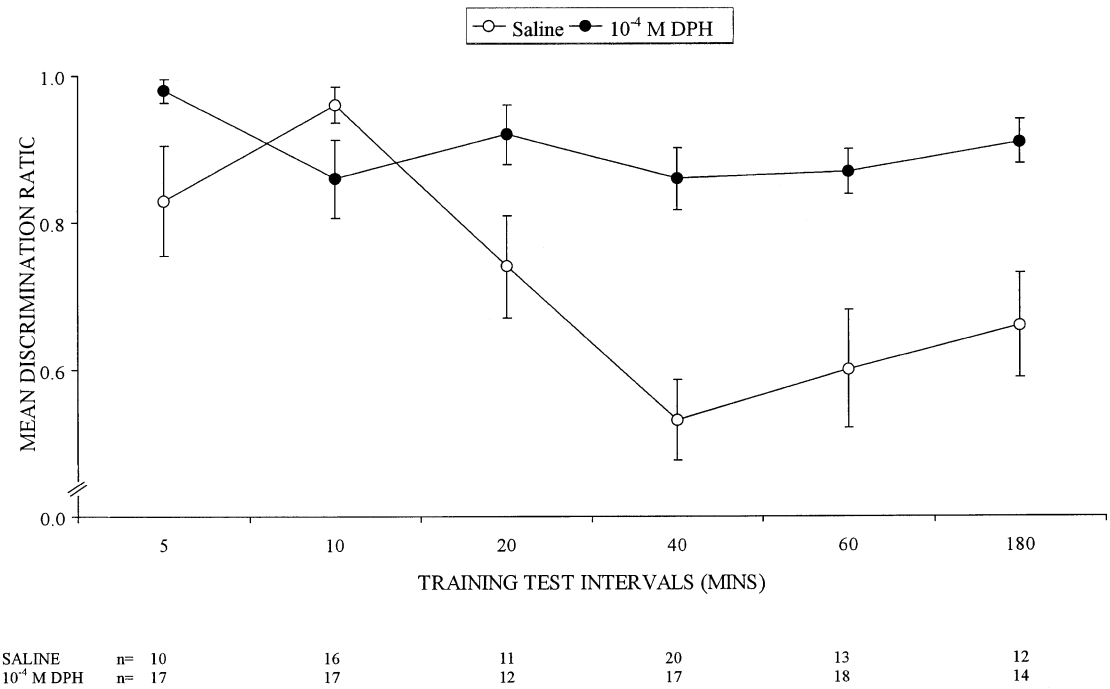

Fig. 3. The effect of treatment with DPH on mean DR (±S.E.M.). Chicks were pretreated with OT and EtOH, injected 24 and 48 h prior to pretraining, and treated with either DPH or NaCl. Chicks were tested at 5, 10, 20, 40, 60 and 180 min after the training experience.

2.6.1. Method

Chicks ($N = 240$) were divided into two equal groups. All chicks in both groups received a total dose of 2.5-mg OT (dissolved in saline), followed by two injections of 154-mM NaCl, over 2 days. On Day 3 of the experiment, 1 h prior to the initiation of the pretraining phase, each chick was administered an injection of 1.0-mg TH and given ad lib access to chick mash. All injections were administered in a 100-μl volume. Chicks were then trained on the one trial passive avoidance task.

Immediately after training, half of the chicks (120 birds in total) were injected with 10^{-4}-M DPH, while the remaining birds (120 chicks in total) were injected with saline (154-mM NaCl). Twenty chicks from both the DPH-treated and saline control groups were assessed for their recall of the training experience 5, 10, 20, 40, 60 and 180 min after initial training. The times were chosen to correspond with the different stages of memory as proposed by the three-stage memory model (Gibbs and Ng, 1977; Ng and Gibbs, 1991).

2.6.2. Results and discussion

The results of Experiment 3 are presented in Fig. 3. A two-way (Drug × TTI) between-groups ANOVA, with unweighted means, revealed a significant drug main effect [$F_{(1,165)} = 37.48$, $P < .001$], a significant TTI main effect [$F_{(5,165)} = 6.60$, $P < .001$] and a significant Drug × TTI interaction effect [$F_{(5,165)} = 5.13$, $P < .001$]. Simple main effects analysis revealed that there was a significant difference across the TTIs for the saline group [$F_{(5,176)} = 10.68$, $P < .001$]. No significant difference was found across the TTIs for the DPH group. Furthermore, simple main effects analysis revealed significant differences at 20 [$F_{(1,176)} = 4.91$, $P < .05$], 40 [$F_{(1,176)} = 26.72$, $P < .001$], 60 [$F_{(1,176)} = 15.47$, $P < .001$], and 180 min [$F_{(1,176)} = 11.08$, $P < .01$]. No significant differences were found at 5 or 10 min following training.

The results of Experiment 3 indicate that DPH administered immediately following the training experience ameliorated retention deficits from 20 min posttraining when compared to saline controls. In addition, it can be seen that pretreatment with OT/ethanol produced a loss of ITM and LTM, while STM remained intact. The finding of no difference in retention of memory at 5 and 10 min post-training suggests that the STM phase of memory is not susceptible to the effects of OT/ethanol pretreatment.

3. General discussion

The results of the three experiments demonstrate that (a) thiamine deficiency induced by the administration of OT, coupled with ethanol administration, produces memory dysfunction with loss of ITM and LTM and spared STM; (b) DPH overcomes the effect of OT and ethanol on memory with a dose of 10^{-4} M, yielding better memory retention; and (c) DPH is able to counteract the effects of combined OT and ethanol exposure on memory, sometime after 10 min post training. This is the time of the development of the ITM stage in the Gibbs and Ng memory model (Gibbs and Ng, 1977; Ng and Gibbs, 1991).

The results suggest that thiamine deficiency plays an important role in the processes that underlie memory formation. Furthermore, when the avitaminosis is coupled with exposure to ethanol, a more permanent memory dysfunction occurs. Specifically, exposure to OT and ethanol in the neonate chick appears to exert its deleterious effects in the formation and or maintenance of the ITM stage of memory and, as a consequence, the succeeding stage long-term memory. These findings are consistent with previous findings that pretreatment with OT results in the deterioration of memory retention sometime following 10 min postlearning (Crowe and Kempton, 1997; Stojanovska, 1993) and that this coincides with the ITM stage (Gibbs and Ng, 1977; Ng and Gibbs, 1991).

Results from the current study suggest that the combination of thiamine deficiency and ethanol exposure lead to a memory impairment that is irreversible following thiamine resupplementation, unlike the deficit induced by OT alone (Crowe and Kempton, 1997). Furthermore, research in our laboratories has shown that alcohol alone does not appear to impair memory (Crowe and Kempton, 1997) and that the deficit produced by OT alone appears at the same time as the deficit produced by OT and ethanol in combination—after 10 min postlearning (Crowe and Kempton, 1997; Stojanovska, 1993). Consequently, it appears that the processes that underlie memory formation are permanently compromised following thiamine deficiency coupled with ethanol exposure.

According to the Gibbs and Ng (Gibbs and Ng, 1977; Ng and Gibbs, 1991) model of memory, Na^+/K^+ ATPase activity is involved in the initiation of the ITM stage and any inhibition of ITM has consequences for the consolidation of the subsequent stage of memory (i.e., the LTM stage). Therefore, it may be that the effects of thiamine deficiency in association with ethanol noted in this study may produce their effects on memory function as a result of inhibition of the sodium pump, with amnesia first appearing after 10 min postlearning and lasting for as much as 24 h after the training experience (Crowe and Kempton, 1997). Previous investigations have suggested that Na^+/K^+ ATPase activity is implicated in the memory deficit induced in the chick by thiamine deficiency in association with ethanol neurotoxicity (Crowe and Kempton, 1997; Stojanovska, 1993). Na^+/K^+ ATPase is believed to play an important role in the active transport of thiamine by providing energy through the hydrolysis of ATP. Furthermore, Na^+/K^+ ATPase can be decreased by exposure to ethanol or ouabain (Hoyumpa, 1980; Thomson et al., 1983). Although the exact role of the Na^+/K^+ pump in the brain remains unclear, it is generally agreed that the functions regulated by the enzyme include maintaining the membrane potential, ion transport and the

transport of organic molecules such as glutamate (Rawn, 1989). Consequently, it can be anticipated that any major disturbances of the enzyme would have widespread effects on the functioning of the CNS.

The literature remains sparse about the effects of ethanol on Na^+/K^+ ATPase, even though the importance of Na^+/K^+ ATPase activity to memory formation has been widely accepted. One possible way in which ethanol may exert its effects on Na^+/K^+ ATPase may be by facilitating the effects of the catecholamines, thus causing an activation of Na^+/K^+ ATPase (Cheng et al., 1977). An enhancing effect of ethanol on Na^+/K^+ ATPase activity as proposed by Cheng et al. (1977) may explain why ethanol, when administered alone, does not produce any memory deficits.

It is premature to suggest which mechanisms are actually impaired or damaged when thiamine deficiency is combined with acute alcohol administration. However, what is clear is that the combination of these agents leads to memory dysfunction that is not reversible by thiamine resupplementation. The experiments reported in this series of studies demonstrate that thiamine deficiency produced pharmacologically with OT, coupled with the acute administration of ethanol, can adversely affect memory processing in the neonate chick and that this deficit can be reversed by the application of DPH. However, more research is needed to delineate the exact contributions of Na^+/K^+ ATPase and DPH to memory function including direct physiological measures of the enzyme in a variety of activation states. This series of studies is currently underway in our laboratory.

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