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Lipopolysaccharide induces memory-processing deficits in day-old chicks

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Abstract

Recent evidence has demonstrated that immune activation can result in cognitive deficits due to the actions of the proinflammatory cytokines. These series of studies examined the effects of peripheral administration of lipopolysaccharide (LPS) on the memory processes of day-old chicks trained on a single-trial passive-avoidance task. LPS impaired performance in a dose- and time-dependent manner. Maximal impairment was produced by a dose of 2.5-mg/kg LPS administered 60 min prior to training. Retention tests revealed that deficits in memory processing appeared between 10 and 20 min posttraining. These results demonstrate an inhibitory effect of LPS on memory processing at the transition point from short-term memory to intermediate-term memory.

Keywords: Chick; Cytokines; Learning; Lipopolysaccharide; Memory; Sickness

1. Introduction

To combat infection and injury, organisms undergo a range of physiological and behavioural changes including fever, decreased food and water intake, decreased social exploration, and increased slow wave sleep (Hart, 1988). These responses are collectively known as sickness behaviour (Kent et al., 1992a). Anecdotal and experimental evidence suggests that colds and influenza also produce cognitive deficits in humans (Smith, 1992). While the mechanisms underlying the cognitive effects of sickness are as yet unknown, they are presumed to be due to the central actions of the proinflammatory cytokines.

Lipopolysaccharide (LPS) is the active fragment of gram-negative bacteria. When injected systemically or centrally, LPS mimics the effect of live bacteria and induces sickness behaviour (Kent et al., 1992b; Kluger, 1991; Layé et al., 1994). This effect is attributed to the cascade of cytokine synthesis and release from macrophages and other related cell types that is triggered by LPS. The primary proinflammatory cytokines induced by LPS are interleukin (IL)-1β, IL-6, and tumour necrosis factor α (TNF-α).

LPS has been used to induce sickness behaviour in several animal models to assess the link between immune activation and cognition. Intraperitoneal injection of LPS impairs contextual, but not auditory-cue, fear conditioning in rats (Pugh et al., 1998). The selectivity of this impairment is indicative of disruptions in hippocampal processing, as hippocampal lesions have previously been shown to produce the same pattern of results (Phillips and LeDoux, 1994). Further, pretreatment with IL-1 receptor antagonist (IL-1ra) prevented the LPS-induced impairment in contextual fear conditioning. Thus, the authors suggest that IL-1 acting on the hippocampus plays a role in the LPS-induced impairment. It has also been reported that direct injection of LPS into rat hippocampus impairs spatial learning and memory in two other tasks, the Morris water maze (MWM) and the Y-maze when tested between 10 and 17 days later (Yamada et al., 1999). Interestingly, nonspatial long-term memory (LTM) as assessed by a passive-avoidance test was not affected by hippocampal injection of LPS. In two similar studies, bilateral hippocampal infusion of LPS or IL-6 impaired the acquisition and retention of an active avoidance task in the rat when tested 10–21 days later (Ma and Zhu, 1997a,b). Avoidance learning is also thought to involve the hippocampus (Lipp et al., 1984).

IL-1β administered intraperitoneally to mice (Gibertini et al., 1995) and into the cerebral ventricles in rats (Oitzl et al., 1993) also produces spatial learning and memory deficits on the MWM. Mice infected with *Legionella pneumophila* demonstrate spatial learning deficits on the MWM, which were reversed by treatment with anti-IL-1β antibodies,

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suggesting that they are due to the presence of circulating IL-1β (Gibertini et al., 1995). In a follow-up study, it was reported that IL-1β only impaired MWM performance when the starting position of the animals was varied, but not when they entered at a fixed position (Gibertini, 1996). Learning under the random-start protocol is thought to be hippocampally dependent, while that in the fixed-start protocol is not (McNamara and Skelton, 1993). Thus, the most parsimonious explanation of these results is that hippocampal functioning is diminished in sick animals, disturbing their ability to learn complex relations in their environment, but not simpler motor procedures.

The current study investigated the effects of peripheral immune activation induced by LPS administration on the memory processes of day-old chicks using a single-trial passive-avoidance task. LPS induces hyperthermia and sickness behaviour, including fever, reduced food intake, and increased somnolence in the chicken when administered either peripherally or centrally (Johnson et al., 1993). A large amount of previous experimentation conducted with day-old chicks has provided valuable information regarding biochemical stages underlying memory formation following learning on the passive-avoidance task (Andrew, 1991; Gibbs and Ng, 1977; Rose, 2000).

The Gibbs and Ng's (Gibbs and Ng, 1977; Ng and Gibbs, 1991) model of memory formation consists of three sequentially dependent stages. Short-term memory (STM) is thought to last for 5–10 min following learning, and its formation is attributed to neuronal hyperpolarization arising from an activity-induced increase in potassium conductance. A second stage, intermediate-term memory (ITM), lasts from 20 to 50 min postlearning. The formation of ITM is attributed to neuronal hyperpolarization induced by the electrogenic sodium/potassium (Na^+/K^+ ATPase) pump. Sodium pump blockers, such as the cardiac glycoside ouabain, inhibit the formation of ITM and induce retention deficits apparent 15 min postlearning. This stage consists of two distinct phases, ITM(A) and ITM(B), which possess distinct temporal parameters and are susceptible to inhibition by different compounds. ITM(A) is energy-dependent and is susceptible to blockade by the ATP synthesis inhibitor 2,4-dinitrophenol (DNP), whereas ITM(B) is not susceptible to DNP blockade. It is believed that the neuronal events that trigger the transition from ITM(A) to ITM(B) give rise to cellular activities that culminate in LTM. This final stage is defined as retention beyond 60 min postlearning, and is thought to be dependent on protein synthesis. These temporal parameters are consistent with behavioural observations demonstrating that retention of the task consists of three distinct stages of high levels of retention separated by two points of transient retention deficit, one at 15 min and the other at 55 min, which presumably occur as one stage develops into the next.

Three separate experiments were conducted in the present report. The first determined the optimal dose at which LPS induced memory deficits, the second ascertained the time required for LPS to impair memory, and the third determined the stage in memory formation when deficits become apparent.

2. Methods

2.1. Animals

Day-old black Australorp white Leghorn 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 in each pair was marked with a small black stripe on its head for identification purposes during data recording. Ambient temperature was maintained at 25–29°C with a 25-W incandescent globe suspended above each box. Each experimental group consisted of an initial sample of 20 chicks.

2.2. Drugs

All drugs were administered by subcutaneous injection with a 27.5-gauge needle into a ventral skin-fold just below the rib cage. LPS from *Escherichia coli* serotype 0111:B4 (Sigma–Aldrich, Castle Hill, Australia) was dissolved in sterile isotonic saline to the required concentration and injected in a volume of 100 μl per chick.

2.3. General procedure

The single-trial passive-avoidance task utilises the spontaneous tendency of chicks to peck at objects in their immediate environment. As part of the pretraining trial, chicks were initially trained to peck at a small chrome bead dipped in water, which increases the probability of the chicks pecking on the training trial. Following an interval of approximately 20 min, each pair of chicks was presented with a red, and then a blue bead dipped in water. The number of pecks and latency to first peck for each bead were recorded on an electronic handset. For the training trial, a red bead was dipped in methyl anthranilate (MeA) and presented to each pair for 10 s. MeA has an unpleasant taste, which elicits aversive reactions in the chicks such as shaking their heads and wiping their beaks on the floor immediately after pecking. The bead was presented once, and the number of pecks was recorded. Chicks failing to peck at the red bead were excluded from later analysis. To test for retention of the task, chicks were presented with a dry red bead followed by a dry blue bead, and the number of pecks at each was recorded. Retention was indexed as a discrimination ratio (DR) between the number of pecks at the nonaversive (blue) bead and the number of pecks at both the aversive (red) and nonaversive beads. The use of the DR minimises the impact of any differences in the number of pecks. Chicks failing to peck at the blue bead during the retention trial were excluded from analysis, as a failure to

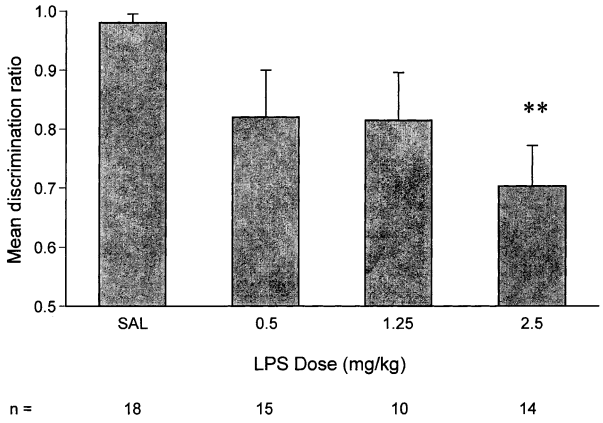

Fig. 1. The effect of various doses of LPS on retention, calculated as a DR (±S.E.M.). ** $P<.01$ compared to saline.

discriminate the aversive and nonaversive beads is indicative of a generalised avoidance response rather than discriminated memory, and thus renders the DR indeterminate (Ng and Gibbs, 1991). The final number of chicks in each group is presented at the bottom of each figure.

2.4. Dose response study

LPS (0.5, 1.25, 2.5, or 5 mg/kg) or saline was administered 60 min prior to training on the passive-avoidance learning task. Performance of each of the groups was compared at 180 min postlearning.

2.5. Administration time study

In order to determine the optimal time of administration of LPS, chicks were injected with the most appropriate dose of LPS as determined by the dose response study (2.5 mg/kg) or saline 0 (i.e., immediately after training), 60, 120, or 240 min prior to training on the passive-avoidance task. Performance was compared at 180 min postlearning.

2.6. Retention time study

To determine the stage in memory processing where deficits become apparent, LPS (2.5 mg/kg) or saline was administered to a cohort of chicks at the optimal time (60 min) before training as determined by the administration time study. Chicks were tested for retention at training-time intervals (TTIs) of 5, 10, 20, 40, 60, and 90 min.

2.7. Data analysis

All data are presented as mean ± S.E.M. ANOVA was used to examine differences between the mean DRs, as well as the mean number of pecks at the beads on the retention trial for each experimental group to determine whether LPS induced a performance-specific deficit or simply a depression in responding. One-way ANOVA was used to examine differences between the treatment groups in the dose response study. Two-way ANOVA was used for the administration time [Drug (2) × Time of injection (4)] and retention time [Drug (2) × TTI (6)] studies.

3. Results

3.1. Experiment 1: LPS dose response

The lower doses of LPS impaired performance in a dose-dependent manner (Fig. 1). ANOVA indicated a significant effect for dose of LPS [$F(3,56)=3.83$, $P<.025$]. Post-hoc Dunnett's tests revealed that chicks injected with 2.5-mg/kg LPS differed from controls (mean DR = 0.70 ± 0.07 vs. 0.98 ± 0.01, $P<.005$). Thus, 2.5 mg/kg was chosen for all subsequent experiments. ANOVA revealed that there was no difference in the mean number of pecks on the retention trials for each of the treatment groups [$F(3,159)=0.73$]. All but four of the chicks receiving the 5-mg/kg dose of LPS had to be excluded from the data analysis due to their failure to peck at either the red bead on the training trial or the blue bead on the retention trial. Behavioural observations indicated that chicks receiving this dose appeared drowsy and tended to ignore the bead presented to them. Chicks receiving the lower doses of LPS, on the other hand, were more alert and were more capable of performing the task. The highest dose was therefore deemed invalid due to the marked effects on alertness and orientation, and was thus excluded from the analysis.

3.2. Experiment 2: administration time

The LPS-induced memory deficits are time-dependent (Fig. 2). ANOVA yielded significant main effects for drug [$F(1,117)=11.63$, $P<.001$] and time of injection [$F(3,117)=3.44$, $P<.025$], as well as their interaction [$F(3,117)=4.22$, $P<.01$]. Simple main effects analysis

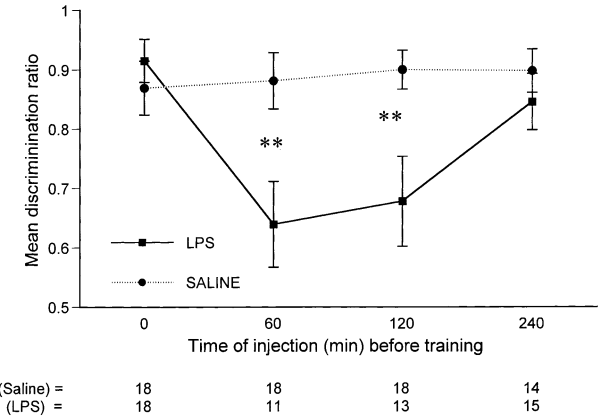

Fig. 2. The effect of 2.5-mg/kg LPS administered at various times before training on the mean DR (±S.E.M.). ** $P<.01$ compared to saline.

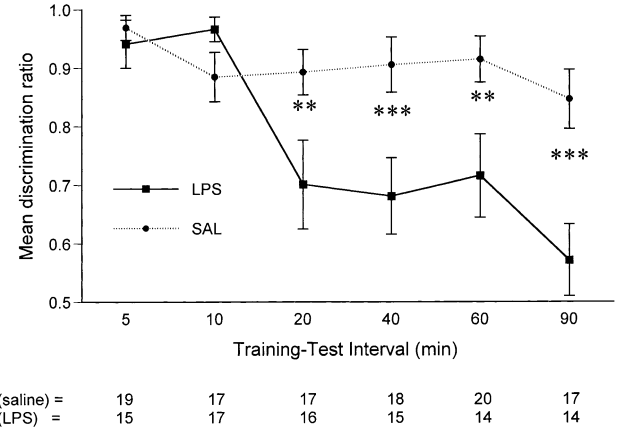

Fig. 3. The effect of LPS (2.5 mg/kg 60 min prior to training) on the mean DR (±S.E.M.) at various training-test intervals following training. ** $P<.01$, *** $P<.001$ compared to saline.

revealed significant differences for injection times of 60 [$F(1,115)=11.07$, $P<.005$] and 120 [$F(1,115)=10.33$, $P<.005$] min prior to training. LPS administered 60 min prior to training yielded the lowest mean DR compared to control procedures for the same time frame (0.64 ± 0.07 vs. 0.88 ± 0.05). There were no differences between the mean number of pecks on the retention trials for saline- and LPS-treated chicks, as revealed by the absence of a significant main effect of drug [$F(1,312)=0.29$] or an interaction between drug and administration time [$F(3,312)=1.13$].

3.3. Experiment 3: retention time

Retention levels were comparable to controls for the first 10 min postlearning, after which time retention was impaired (Fig. 3). ANOVA revealed a significant main effect for drug [$F(1,187)=24.20$, $P<.0005$], TTI [$F(5,187)=6.93$, $P<.0005$], and their interaction [$F(5,187)=3.91$, $P<.005$]. Simple main effects analysis revealed significant differences at 20 [$F(1,183)=9.87$, $P<.005$], 40 [$F(1,183)=13.41$, $P<.001$], 60 [$F(1,183)=10.62$, $P<.005$], and 90 [$F(1,183)=18.83$, $P<.001$] min posttraining. After 20 min, mean DRs for LPS (0.57–0.70) were well below those of controls (0.85–0.92). Again, there were no differences between the mean number of pecks on the retention trials for chicks injected with saline and LPS, as revealed by the lack of a main effect of drug [$F(1,468)=0.74$] or an interaction between drug and TTI [$F(5,468)=0.37$].

4. Discussion

Previous research has demonstrated that immune activation results in cognitive deficits in laboratory rodents. The present study is the first to demonstrate such deficits in the day-old chick on the passive-avoidance task. The results of the first two experiments indicate that a dose of 2.5-mg/kg LPS administered 60 min prior to training on the passive-avoidance task produces optimal retention deficits when tested at 180 min postlearning. LPS-injected chicks showed retention levels similar to those of controls between 5 and 10 min postlearning, but exhibited sharp declines thereafter. Retention of the task was significantly impaired by 20 min after learning. The absence of any significant differences between the number of pecks on the test trials indicates that these impairments were not simply the result of malaise or decreased motivation associated with immune activation, but are performance-specific deficits.

Interpreted in terms of the Gibbs and Ng's (1977, 1991) memory model, these findings suggest that LPS may disrupt the formation of ITM, and therefore consolidation of LTM, leaving STM intact. Previous research has indicated that sodium pump blockers, such as the cardiac glucoside ouabain and DNP, also inhibit the development of ITM (Gibbs and Ng, 1977), thus, the results of this study suggest the possibility that LPS may interfere with Na^+/K^+ ATPase activity and ATP synthesis.

The present finding is inconsistent with the observations of Yamada et al. (1999), who reported that LPS did not produce deficits on a passive-avoidance task. Rats in that study, however, were trained 16 days and tested 17 days following bilateral LPS administration directly into the hippocampus on a task where animals received a footshock if they crossed in a darkened compartment of a shuttle box. Due to the methodological differences between the two investigations, comparison between the results is problematic.

Most previous research seems to suggest a role for the hippocampus in LPS- and cytokine-induced cognitive deficits. Although two forebrain areas, the left intermediate medial hyperstriatum ventrale and the lobus parolfactorius, are proposed to be the most important in passive-avoidance learning in chicks (Patterson et al., 1986), the hippocampus has also been implicated. Specifically, pretraining lesions to the hippocampus in day-old chicks result in retention deficits when tested at 3 h (Sandi et al., 1992). In addition, although peripherally administered LPS does not enter the brain itself, it does induce the expression of IL-1β, IL-6, and TNF-α at the gene and protein level in various brain regions including the hippocampus (Layé et al., 1994; Van Dam et al., 1991). Consequently, it is possible that deficits in the current study may have been due to a LPS-induced disruption in hippocampal functioning.

Previous research indicates that it is not LPS itself, but the proinflammatory cytokines it induces, which communicate with the central nervous system and lead to the neural changes that are responsible for cognitive impairment (Pugh et al., 1998). For this reason, the physiological and behavioural effects of LPS are preceded by a latent period (usually 30–90 min) after peripheral administration (Bluthé et al., 1992; Kent et al., 1992b; Luheshi et al., 1996; Roth et al., 1993). Experimental evidence has revealed that serum IL-1 begins to increase 1 h after peripheral LPS administration (Zuckerman et al., 1989), serum TNF increases 30–

45 min after peripheral injection of LPS (Zuckerman et al., 1989), and serum IL-6 is increased by 1 h post-LPS injection (Roth et al., 1993). That LPS did not produce a deficit when administered immediately following the training trial may suggest that the proinflammatory cytokines responsible for the memory-processing deficit observed at other administration times were not released in sufficient quantities to alter neural functioning until after a permanent memory trace had already been formed.

It has been proposed that LPS, IL-1β, and IL-6 exert their disruptive effects on spatial learning and memory by inhibiting long-term potentiation (LTP) in the hippocampus. LTP is a form of synaptic plasticity that has been proposed as a biological substrate for learning and memory. IL-1β has been found to inhibit LTP in the rat hippocampus in a number of studies (Bellinger et al., 1993; Coogan et al., 1991; Cunningham et al., 1996; Katsuki et al., 1990; Luk et al., 1999), as has IL-6 (Li et al., 1997), IL-2 (Tancredi et al., 1990), interferon (D'Arcangelo et al., 1991), TNF-α (Cunningham et al., 1996), and LPS (Cunningham et al., 1996). LTP induction is triggered by an increase in intracellular calcium concentration occurring through the *N*-methyl-D-aspartate (NMDA)-associated calcium channel. Cunningham et al. (1996) not only demonstrated that the inhibitory effect of IL-1β could be attenuated by administration of IL-1ra, but that IL-1β inhibits the increase in calcium influx occurring in LTP. Consequently, it is suggested that IL-1β-induced inhibition of LTP may derive from an inhibitory effect on calcium channels.

From an evolutionary perspective, fever and sickness behaviour are believed to be part of an adaptive response, which increases the chances of survival during inflammatory challenge (Hart, 1988). It makes sense, then, to ask whether there is any adaptive value to the cognitive impairment associated with sickness behaviour. Maier and Watkins (1998) suggest there may be no real adaptive purpose. Instead, it may be that the same hippocampal neurons participate in some aspects of both learning and memory and the organisation of sickness behaviour, thus, to the extent that hippocampal neurons are demanded by peripheral immune stimulation to participate in the organisation of sickness, the neurons may be less able to participate in their cognitive functions. Gibertini et al. (1995), on the other hand, suggest that the cognitive deficit may be an indirect extension of the primary objective of fever and sickness behaviour, which is to minimise mobility during infection.

The present study has demonstrated that LPS disrupts memory processing in day-old chicks trained on the passive-avoidance task. As LPS induces several cytokines including IL-1β, IL-6, and TNF-α, we cannot specify which proinflammatory cytokine, or combination, is responsible for the observed deficits. Although the biological actions of these cytokines overlap, each has its own characteristic properties (Dantzer et al., 1998). Clearly, the roles of the individual cytokines, such as IL-1β, IL-6, and TNF-α, on the memory processes of young chicks should be further investigated. These studies are currently under way in our laboratory.

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