

Immunoglobulin-Mediated Neuro-Cognitive Impairment: New Data and a Comprehensive Review

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Abstract Excessive influx of immunoglobulin (IgG) into the brain has been reported to induce central nervous system (CNS) dysfunction. Depressed patients may exhibit immune activation manifested by elevated inflammatory markers and pro-inflammatory cytokines. The brain and especially the limbic system contain high concentrations of high affinity Fc receptors. We reviewed the literature on this phenomena and present data on the behavioral effects of pooled normal IgG on the brain. Many disease states are associated with depression and we examined whether this may be linked to high IgG influx. Female Balb/C mice were injected intracerebroventricularly with human immunoglobulin whole molecule, or human IgG F(ab')₂ or Fc fragments. Control mice were injected with saline. The four groups were subjected to behavioral (staircase, forced swimming test, and elevated plus maze) and cognitive tests (passive avoidance test). IgG-injected mice exhibited depression-like behavior as reflected by significantly higher immobility time in the forced swimming test ($p<0.05$) and hyperactive behavior as

reflected by higher number of stairs climbed in the staircase test compared to controls ($p<0.01$). Fc-fragments-injected mice showed hyperactive behavior as reflected by both higher number of stairs climbed and rearing events in the staircase test compared to controls. The results indicate that high levels of normal IgG in the cerebrospinal fluid can cause hyperactivity and depression-like behavior. The mechanism involved in these CNS manifestations include possibly Fc receptor binding.

Keywords Immunoglobulin G · Fc receptor · Inflammation · Depression · Sickness behavior

Introduction

Immunoglobulin G (IgG) is the main antibody isotope found in the serum. Increases in IgG levels in the blood are seen during acute or chronic infection, inflammatory disorders, autoimmune disorders, and some tumors [1–6]. IgG works through its variable region (Fab')₂ and through its crystallizable region (Fc). Through the Fab region, IgG identify and neutralize a wide range of foreign objects including bacteria, viruses, and super-antigens. Through the Fc region, IgG binds to the Fc receptor and internalizes into the cell where it activates a variety of cellular process which have important roles in inflammation and immunity, including proteases and cytokines release and oxidative burst [7, 8]. Fc receptors for IgG (FcγR) belong to the immunoglobulin gene superfamily [9]. FcγR exist in three classes: FcγRI, FcγRII, and FcγRIII [10, 11]. Subtypes FcγRI, FcγRII, and FcγRIII are prevalent on microglial cells, where FcγRII are detected in the hippocampus and the cerebellum [12, 13]. The present study will review the literature on the link between immunoglobulins,

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inflammation, depression, and sickness behavior. We also show the effects of immunoglobulins injection to the brain on neuro-cognitive performance in mice.

Peripheral inflammation can provoke leakage of the blood–brain barrier (BBB) and extravasation of serum proteins, including IgG, into the brain [14–17]. Several studies explored the cellular consequences of brain exposure to serum proteins [14, 15, 18]. Mice injected with complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IFA) exhibit significant increased IgG levels in the cervical spinal cord and the brainstem compared to controls. In addition, there is an increase in immunolabeling of microglial cells [18]. We also found that mice immunized subcutaneously with CFA display cognitive decline compared to naïve mice [19]. Depression and memory impairment are some of the characteristics of chronic fatigue syndrome (CFS) [20, 21]. In CFS antibodies to diverse cell nuclear components, phospholipids, neuronal components, neurotransmitters, as well as antibodies against some neurotransmitter receptors of the central nervous system (CNS) have been described [22–27]. One of the main CNS inflammatory diseases is multiple sclerosis (MS). Depression is one of the main determinants of quality of life in MS patients [28]. Increase in the CSF-IgG levels is included in MS diagnostic criteria [29].

Previous studies have shown an association between antibodies and brain dysfunction. Demented antiphospholipid syndrome (APS) patients have higher levels of antiphospholipid antibodies (aPL) compared to non-demented APS patients [30]. Anti-neuronal antibodies are a group of antibodies that react to neuronal components. Antibodies that react to neuronal components associate with neuropsychiatric manifestations in systemic lupus erythematosus (SLE) patients [31, 32]. Cognitive impairment, psychosis, and depression in SLE are associated with many antibodies, including aPL [3, 33, 34]. Possible mechanisms include vascular occlusion and injury by pathogenic antibodies in a disrupted BBB. Antibodies to phospholipids are found to induce behavioral and cognitive effects in mice [19, 35].

Antibodies against *N*-methyl-D-aspartate (NMDA) receptors associate with depressed mood and with a decrease in short-time memory and learning in SLE patients [36]. Encephalitis syndromes have been also associated with antibodies against both neural surface antigens (voltage-gated potassium channel complexes, NMDA receptors) and intracellular antigens (glutamic acid decarboxylase-65), constitute an increasingly recognized group of immune-mediated brain diseases [1, 37]. Recent studies demonstrated the presence of immunoglobulin (Ig) in the brain parenchyma of Alzheimer's disease (AD) tissues and it also is shown that specific neurons that showed degenerative, apoptotic features contained vascular-derived antibodies [38–42]. Anti-neuronal antibodies similar to those found in AD are found to induce memory dysfunction in rats [43, 44]. Clinical manifestations of Parkinson's disease, particularly dyskinesia and depression, are found to be associated with the presence of autoantibodies [45].

Review of Depression, Sickness Behavior, and Inflammation

The link between immunoglobulins, inflammation, depression, and sickness behavior is summarized in Table 1.

Depression

Depression is a mental disorder characterized by depressed mood and loss of interest or pleasure [46]. The prevalence of depression in the total population is 13 % [47]. Over the years the monoamine deficiency hypothesis received the highest focus of research. Accordingly, antidepressants which act on neurotransmitters pathways are the common treatment in depression [46]. However, this hypothesis fails to address all aspects of depression and patients receiving antidepressants fail to achieve full remission. In the recent years inflammation has been linked to depression in several

Table 1 The role of the immune system and IgG in brain inflammation, depression, and sickness behavior

	Role of the immune system and IgG	References
Depression	Medications with an effect on the immune system (e.g., interferon) affect mood	[41, 47]
	Depression is more frequent in patients with diseases having elevated levels of prostaglandins, complement, circulating leukocytes, and cytokines	[43–45]
	High levels of cytokines: TNF- α , IL-6, IL-10	[40, 42, 46]
Sickness behavior	IL-1 and LPS can induce sickness behavior in animals	[49, 50]
	Pro-inflammatory cytokines levels, including TNF- α , IL-1 α , IL-1 β , IL-6, and INF γ , are elevated	[48]
Brain inflammation	Increases in IgG levels during acute or chronic infection, inflammatory disorders, and autoimmune disorders	[1–6]
	Activation of macrophages and through Fc receptors leads to proteases and cytokines release and oxidative burst	[7, 8]

ways. Depressed patients often exhibit immune activation [48–55]. Depression is more frequent in patients with diseases having inflammatory markers, such as prostaglandins, complement circulating leukocytes and cytokines [51–53]. Medications with an effect on the immune system (e.g., interferon) can affect mood [49, 55]. Levels of pro-inflammatory cytokines, including tumor necrosis factor α (TNF- α), interleukins (IL) 1 and 6 are elevated during a depressive episode [48, 50, 54].

Sickness Behavior

Sickness behavior occurs in animals and humans, in a response to inflammation or infection. It is characterized by weakness, malaise, reduced food and fluid intake, decreased interest in surroundings, lethargy, fever, and increased sleep [56]. Administration of endotoxin (LPS) or IL-1 to animals induces a behavioral pattern which resembles sickness behavior [57]. Although IL-1 is sufficient to induce sickness behavior, it is not necessary and other factors contribute to the behavioral changes [58]. There are several similarities between sickness behavior and the symptoms of depression. Similar to depression, pro-inflammatory cytokines including TNF- α , IL-1 α , IL-1 β , IL-6, and interferon γ (INF γ) are elevated [56]. Depressed mood, hypomobility, hypophagia (only in typical depression), and hypersomnia (only in atypical depression) also share characteristics of sickness behavior and depression [59, 60]. Due to these similarities it is postulated that cytokines can induce depression or are the cause of depression. Sickness behavior has unique features which are not observed in depression. These include fever, hypersensitivity, and cognitive deficits [61, 62].

IgG and Inflammation

The expression of sickness behavior and depression are complex and probably involve multiple mechanisms beside pro-inflammatory cytokines. Increased IgG levels, during an infection or acute and chronic inflammatory conditions, can contribute to the development of sickness behavior and depression in several ways. IgG can enter into the brain and bind to Fc receptors which are expressed on microglia cells [63, 64]. Activation of microglia through Fc receptors can induce local inflammation within the brain which may lead to synthesis of cytokines, neurological dysfunction, and behavioral effects [63, 65]. As mentioned above, Fc γ R2 is expressed in the hippocampus and in the cerebellum. In the hippocampus Fc γ R2 is expressed on parvalbumin-GABAergic expressing interneurons localized at the pyramidal cells layer [13]. The hippocampus function is related to emotion, learning, and memory and has also been extensively implicated in the pathogenesis of depression [66, 67]. Binding of IgG to Fc γ R2 can contribute to behavioral

changes seen in depression and sickness behavior. A recent study found enhanced levels of nonspecific IgG in the brain of mice with a non-normal social behavior. The IgG was deposited in the cortex, hippocampus, striatum, hypothalamus, substantia nigra, and the cerebellum [68]. A high percentage of activated microglia cells is also found [68].

In the present study, we examined the behavioral effects of nonspecific normal IgG on the brain. Mice were intracerebroventricularly (ICV) injected with human IgG and were subjected to behavioral and cognitive tests. A definite link with depression behavior was found and a link with Fc receptors was also found.

Materials and Methods

Mice

Female Balb/C mice, aged 8 weeks, were obtained from animal resources, Sackler Medical School, Tel-Aviv University. The mice were raised at the Sackler Medical School Animal Facility under standard conditions, 23 $\pm$ 1 °C, 12 h light cycle (7 am $\pm$ 7 pm) with ad libitum access to food and drink. The Tel Aviv University Animal Welfare Committee approved all procedures.

Study Design

The mice were divided into four groups, each group included ten mice. The first group was ICV-injected with human IgG whole molecule (ChromPure Human IgG whole molecule, Jackson ImmunoResearch, 6.8 μ g/ μ l), the second group was ICV-injected with human IgG F(ab')₂ fragments (ChromPure Human IgG F(ab')₂ fragments, Jackson ImmunoResearch, 4.7 μ g/ μ l), the third group was ICV-injected with human IgG Fc fragments (ChromPure Human IgG Fc fragments, Jackson ImmunoResearch, 2 μ g/ μ l), and the fourth group was ICV-injected with saline. The IgG whole molecule, F(ab')₂ and Fc fragment concentrations were determined according to their molecular weights (160 KD, 110 KD, and 50 KD, respectively). The four groups were subjected to behavioral and cognitive tests as follows: the staircase test (day 5 post injection), the elevated plus maze test (day 6 post injection), the passive avoidance test (days 7 and 8 post injection), and the forced swimming test (FST, day 13 post injection with pretest session).

Passive Transfer

Mice were anesthetized with an intraperitoneal (i.p.) injection of equithesine (4 % chloral hydrate, 6 % sodium pentobarbital). The skull was carefully exposed, and a small hole was drilled with a 25-gauge needle above the right

lateral ventricle (2 mm lateral to the midline and 2.5 mm posterior to the bregma). A 27-gauge needle attached to a Hamilton syringe was inserted at this point to a depth of 2 mm, where preliminary tests confirmed accurate ICV placement by injection of dye. One microliter of IgG was then slowly infused, the needle was withdrawn, and the skin over the scalp was sutured.

Forced Swimming Test

Mice were gently placed in individual glass beakers (height 25 cm, diameter 18 cm) containing water 15 cm deep at 25 °C. On day 1, mice were placed in the cylinder for a pretest session of 15 min, and then removed from the cylinder, allowed to dry in a small cage placed under a source of heat for 10 min, and returned to their home cages. Twenty-four hours later (day 2), the mice were re-exposed to the swimming condition in a similar environment, and then subjected to a test session for 6 min. The behavioral measure scored was the duration (in seconds) of immobility, defined as the absence of escape-oriented behaviors such as swimming, jumping, rearing, sniffing, or diving, recorded during the 6-min test. An increase in immobility time was interpreted as an increase in depression-like behavior.

Staircase Test

Behavioral functions were tested in a staircase test. This test combines measurements of locomotor activity (stair-climbing) and anxiety and exploratory behavior (rearing). The staircase maze consisted of a PVC enclosure with five identical steps, 2.5×10×7.5 cm. The inner height of the walls was constant (12.5 cm) along the whole length of the staircase. The box was placed in a room with constant lighting and isolated from external noise. Each mouse was tested individually. The animal was placed on the floor of the staircase with its back to the staircase. The number of stairs climbed and the number of rears were recorded for a 3-min period. Climbing was defined as each stair on which the mouse placed all four paws; rearing was defined as each instance the mouse rose on hind legs (to sniff the air), either on the stair or against the wall. The number of stairs descended was not taken into account. Before each test the box was cleaned with a diluted alcohol solution to eliminate smells.

Passive Avoidance Test

In order to measure the ability of the mice to remember a foot shock delivered 24 h earlier, a two-compartment enclosure with a shock-grid floor was used. During the first day of testing, the mouse was placed into a smaller, lighted compartment. A door to an adjacent, darkened compartment was opened and the latency up to entry into the darkened

compartment was measured. Upon complete entry into the adjacent chamber, the door was closed and the mouse received a 5-s foot shock. The mouse was then removed from the chamber and returned to its cage. Following a 24-h interval, the mouse was readmitted to the lit chamber, the door was again opened, and the latency up to entry into the adjacent, darkened compartment was measured (to a maximum of 5 min).

Elevated Plus Maze Test

The elevated plus maze was made from polyvinylchloride and built in a ‘plus’ form with two open/white arms (34×7.5×1 cm) and two closed/black arms (34×7.5×17.5 cm) opposing each other. The center of the four arms included middle square (7.5×7.5 cm). The maze was elevated 51 cm height above ground level. Each mouse was placed separately in the center of the maze, facing an open arm, and allowed to freely explore the apparatus for 5 min. Parameters measured included the number of closed and open arms entries, as an index of motor function, and length of time spent in the closed and open arms. An entry was counted only after the mouse entered the arm with four paws. Before each test, the box was cleaned with a diluted alcohol solution to eliminate smells. The percentage of open arms entries out of total arms entries and the percentage of time spent in the closed arms, accepted measures of anxiety levels, were further calculated.

Statistical Analysis

Results are expressed as the mean ± SEM. Statistical analysis was carried out using multivariate one-way analysis of variance (ANOVA). The differences between individual groups were determined using Fisher’s least significant difference post hoc tests (SPSS, Chicago, IL).

Results

Depression-Like Activity in the FST

Depression-like activity as measured by immobility time in the four groups is presented in Table 2. The immobility time of mice injected with human IgG whole molecule, human IgG F(ab')₂ fragments, human IgG Fc fragments, or saline solution differed significantly (306.6±8.9, 274.3±13.6, 258.8±10.3, and 264.5±13.6 s, respectively, $p<0.05$ by ANOVA). The immobility time of IgG whole molecule-injected mice was significantly higher compared to control groups injected either with Fc fragments or saline solution ($p<0.05$ by post hoc LSD). There was a trend toward increase immobility time in IgG whole molecule-injected mice compared to F(ab')₂-injected mice ($p<0.1$ by post hoc LSD). There was no

Table 2 Behavioral and cognitive performance

Group	Forced swimming test Immobility time (max 6 min) (s)	Staircase test Stair-climbing events (in 3 min) (N)	Staircase test Rearing events (in 3 min) (N)	Passive avoidance test Entry latency (max 5 min) (s)	Elevated plus maze test Percent time in closed arms (in 5 min) (%)
ICV human IgG whole molecule	306.6±8.9*	15.6±1.8*	18.4±1.4*	232.3±38.5	66.9±7.9
ICV human IgG F(ab') ₂ fragments	274.3±13.6	10.3±1.4	13.4±2.2	232.2±34.8	52.2±13.2
ICV human IgG Fc fragments	258.8±10.3	14.8±2.0*	23.0±3.5*	145.4±48.9	50.3±12.7
ICV saline control	264.5±13.6	8.8±1.5	14.7±2.0	214.0±36.4	61.4±11.8
	<i>p</i> <0.05	<i>p</i> <0.01	<i>p</i> <0.01	<i>p</i> >0.5	<i>p</i> >0.5

The table summarized depression-like behavior in the FST, behavior in the staircase test, cognitive function in the passive avoidance, and anxiety in the elevated plus maze tests. The immobility time (seconds) in the FST, number of stair-climbing, and rearing events in the staircase test, the latency (seconds) to enter the darkened compartment in the passive avoidance test, and the percent of time spent in the closed arms relative to the total time in the elevated plus maze test in the four groups are presented. *P* values for each variate by one-way ANOVA are presented. * represent significant difference (*p*<0.05) on post hoc analysis compared to control saline group

significant difference between the three control groups (F(ab')₂, Fc, and saline-injected mice).

Hyperactivity and Anxiety in the Staircase Test

Behavioral activity, as measured in the staircase test, of the four groups is presented in Table 2. Overall, there was a significant difference between mice injected with human IgG whole molecule, human IgG F(ab')₂ fragments, human IgG Fc fragments or saline in both stair climbing (15.6±1.8, 10.3±1.4, 14.8±2.0, and 8.8±1.5, respectively, *p*<0.01 by ANOVA) and rearing measures (18.4±1.4, 13.4±2.2, 23.0±3.5, and 14.7±2.0, respectively, *p*<0.01 by ANOVA). Mice injected with either IgG whole molecule or Fc fragments displayed hyperactivity behavior as shown by significantly higher stairs climbed compared to mice injected with saline solution (*p*<0.05 by post hoc LSD). There was a non-significant trend toward increased stair climbing in the IgG-injected mice compared to F(ab')₂-injected mice (*p*<0.1 by post hoc LSD). Post hoc analysis of rearing events revealed significant differences between Fc-injected mice and F(ab')₂ and saline injected mice (*p*<0.05 by post hoc LSD).

Cognitive Function in the Passive Avoidance Test

The latency times to enter the darkened compartment in the four groups are presented in Table 2. No significant difference was found between mice injected with human IgG whole molecule, human IgG F(ab')₂ fragments, human IgG Fc fragments, or saline.

Anxiety in the Elevated Plus Maze Test

Percent of time spent in the closed arms relative to the total time in the four groups, measured in the elevated plus maze, is presented in Table 2. No significant difference was found

between mice injected with human IgG whole molecule, human IgG F(ab')₂ fragments, human IgG Fc fragments, or saline.

Discussion

In the present study, we found that ICV injection of pooled normal human IgG into the brain in mice induces depression-like behavior as reflected by higher immobility time in the FST and hyperactivity behavior as reflected by higher stair climbed in the staircase test. Neither IgG whole molecule nor the other control groups induced cognitive deficits as demonstrated in the passive avoidance test. This is the first report, to our knowledge, of behavioral effects in mice after injection of nonspecific IgG into the brain. The immobility of the mice was not due to a motor deficit, since the mice exhibited normal motor function in the staircase test. Previous studies have shown an association between antibodies and brain dysfunction. Antibodies that react to neuronal components associate with neuropsychiatric manifestations [31, 32]. Antibodies against NMDA receptors associate with depressed mood and with a decrease in short-time memory and learning in SLE patients [36]. Antibodies to phospholipids (aPL) induces behavioral and cognitive effects in mice [19, 35]. In previous study, we found that ICV injection of anti-ribosomal P antibodies into the brain in mice induces depression-like behavior [69]. We found that the immobility time of mice injected with anti-ribosomal P is significantly higher compared to mice injected with nonspecific IgG. The results of the nonspecific IgG and anti-ribosomal P studies may imply on the mechanism by which nonspecific IgG and a specific antibody such as anti-ribosomal P induce depression. Specific antibody such as anti-ribosomal P might induce depression by binding the cell membrane, through the

Fab portion, at high affinity and specificity. A support for the importance of Fab portion is that anti-idiotypic antibodies (anti-ID) injected with anti-ribosomal P antibodies reduce the immobility time in the FST [69]. On the other hand, nonspecific IgG probably induces depression through binding of both the Fc portion and the Fab portion to the cell membrane. Each portion alone binds the cell membrane at low specificity, together the binding affinity and efficiency increase. ICV injection of the Fab fragments did not induce any behavioral effects, indicating that the mechanism involved in these behavioral changes is probably Fc dependent. It is possible that the mechanism of a specific antibody such as anti-ribosomal P antibody also is Fc dependent. The specific binding of the Fab portion to the cell surface might enable a stronger binding between the Fc portion and the Fc receptor. This may lead to a stronger and an extended signal transduction through the Fc receptor and to a significant behavioral effect.

Another possible mechanism by which nonspecific IgG cause behavioral changes might be the activation of microglia. Activation of microglia may cause excessive brain inflammation which leads to neurological dysfunction and behavioral effects. FcγR are expressed on microglia and have an important role in their activation processes [64].

ICV injection of human Fc fragments induced hyperactivity behavior as reflected by both higher number of stairs climbed and rearing events in the staircase test. Contrary to depression, hyperactivity can be induced by binding of the Fc portion to the Fc receptor alone (Fab independent). Another possible distinction between the effects of IgG and Fc fragments could be binding to specific family members of the FcγR which are expressed differentially in the brain. The present findings link behavioral changes with nonspecific antibodies which act in different mechanisms in the brain. The results suggest that unspecific IgG has a role in brain dysfunction and behavioral changes during inflammation probably through Fc receptors. Treatment directed against Fc receptors, such as administration of IVIg, should be considered [70–72].

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