IL RUOLO DEL NERVE GROWTH FACTOR (NGF) NELLO STRESS E COPING DEI RODITORI E DELL’UOMO

Enrico Alleva
(alleva@iss.it)
First, it is impossible to think effectively about depression outside the context of biology. Second, it is impossible to think effectively about depression as only being a matter of biology. Finally, despite the vast quantities of excellent research on which those two conclusions rest, we remain woefully inadequate at effectively treating depression in vast numbers of its sufferers.

Robert M. Sapolsky
Gilbert Laboratory
Department of Biological Sciences
Room MC5020
Stanford, CA, 94305-5020
NERVE GROWTH FACTOR exerts the following actions:

- TROPHIC

- TROPIC

- DIFFERENTIATIVE
Rita Levi-Montalcini and Luigi Aloe
Fig. IV-2. (a) Defensive Upright Posture (Postura Eretta Difensiva); (b) Submissive Upright Posture (Postura Eretta di Sottomissione); (c) Submissive Crouched Posture (Postura Accovacciata di Sottomissione); (d) Aggressive Grooming; (e) Self-Grooming; (f) Freezing.
A valuable indirect method of assessment is the use of wound maps. Species and sex differences are revealed by different targets and by the degree of intensity of offensive patterns. B, back; R, rump; F, flanks; 2, dorsal, eyes, and ears; 3, snout. Lactating females bite at the nearest body part and vulnerable regions, such as head (H) and ventrum (V); females are not inhibited by the usual male inhibitory signals. In contrast, males bite only certain areas (B, R, and F). In golden hamsters areas 2 and 3 are wounded, while cheeks (area 1) are targeted only during juvenile play fighting. See Parmigiani et al. (1988) for mouse wound patterns, Pellis and Pellis (1988) for golden hamster wound patterns, and Pellis (1988) and Blanchard and Blanchard (1981) for wound patterns for rats and other rodent species. (Drawn by S. Bigi.)
Aggressive behavior induces release of nerve growth factor from mouse salivary gland into the bloodstream
(submaxillary salivary gland/adrenal gland)

LUIGI ALOE*, ENRICO ALLEVA†, ARIELA BOHM*, AND RITA LEVI-MONTALCINI*

**FIG. 2.** Time course of NGF release in the bloodstream of fighting mice. Each point represents the mean ± SEM of six mice. Different animals were used for each time point.
\[
\begin{align*}
    r &= 0.89 \\
    y &= -23.04 + 5.88 \times
\end{align*}
\]
### TABLE 1
BEHAVIORAL CHANGES OF DOMINANT AND SUBORDINATE MICE OVER THE 10 FIGHTING SESSIONS

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dominants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tail Rattling</td>
<td>3.3 ± 3.5</td>
<td>2.0 ± 2.4</td>
<td>1.7 ± 2.2</td>
<td>3.0 ± 2.7</td>
<td>2.2 ± 2.2</td>
</tr>
<tr>
<td>Aggressive Grooming</td>
<td>1.1 ± 1.7</td>
<td>0.8 ± 1.6</td>
<td>0.3 ± 1.0</td>
<td>1.0 ± 2.0</td>
<td>1.0 ± 2.1</td>
</tr>
<tr>
<td>Defensive Upright Post.</td>
<td>3.0 ± 3.9</td>
<td>0.2 ± 0.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Crouched Submissive Post.</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Flee</td>
<td>1.4 ± 3.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Freezing</td>
<td>21.6 ± 14.6</td>
<td>15.4 ± 11.1</td>
<td>12.6 ± 11.0</td>
<td>17.0 ± 15.8</td>
<td>19.8 ± 17.9</td>
</tr>
<tr>
<td><strong>Subordinates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tail Rattling</td>
<td>3.5 ± 3.9</td>
<td>1.7 ± 2.9</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Aggressive Grooming</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Defensive Upright Post.</td>
<td>11.9 ± 10.6</td>
<td>11.9 ± 11.1</td>
<td>12.4 ± 5.9</td>
<td>11.8 ± 6.2</td>
<td>12.3 ± 6.0</td>
</tr>
<tr>
<td>Crouched Submissive Post.</td>
<td>1.1 ± 2.1</td>
<td>0.6 ± 1.8</td>
<td>0.5 ± 1.2</td>
<td>1.0 ± 2.1</td>
<td>1.7 ± 4.0</td>
</tr>
<tr>
<td>Flee</td>
<td>13.0 ± 8.7</td>
<td>13.6 ± 6.7</td>
<td>13.5 ± 7.7</td>
<td>13.1 ± 5.6</td>
<td>15.4 ± 9.9</td>
</tr>
<tr>
<td>Freezing</td>
<td>48.9 ± 19.0</td>
<td>62.8 ± 18.1</td>
<td>69.0 ± 24.4</td>
<td>64.8 ± 28.3</td>
<td>72.1 ± 27.2</td>
</tr>
</tbody>
</table>

The data are shown in terms of mean ± S.D. frequencies per individual per test but for freezing, which is shown in terms of mean ± S.D. percent of time per individual per test.
BEHAVIOURAL “STRESS SYNDROMES”
EITHER PRODUCING OR NOT PRODUCING NGF RELEASE INTO THE BLOODSTREAM

<table>
<thead>
<tr>
<th>NON- PSYCHOSOCIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inescapable footshock</td>
</tr>
<tr>
<td>Escapable footshock</td>
</tr>
<tr>
<td>Cold water swimming</td>
</tr>
<tr>
<td>Restraint stress</td>
</tr>
<tr>
<td>Forced biting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSYCHOSOCIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male fighting</td>
</tr>
<tr>
<td>Female fighting</td>
</tr>
<tr>
<td>Pre-copula arousal (F)</td>
</tr>
</tbody>
</table>

*In developing rats unpublished observations indicate a decrease of NGF level and NGF receptor expression in the striatum following cold-water swimming stress while an increase was shown in the hippocampus.
VIDEO-IMAGE ANALYSIS
OF ADRENAL GLAND TISSUES (6-DAY EXPOSURE)

Cortical area

\[ \text{mm}^2 \]

- CYT
- NGF

Medullary area

\[ \text{mm}^2 \]

- 15 μg
- 30 μg
Behavioral modification: corticosterone-enhanced submissive behavior

"subordinate" male

NGF release >> in subordinates

Enhanced release of adrenal products (e.g. corticosteroids)

Adrenal volume >> in subordinates

Functional loop promoting "subordinate" behavior in fighting male mice
SALIVARY NGF RELEASE: EFFECTS ON THE PERIPHERAL NERVOUS SYSTEM

- ACTIVATION OF PNS CELL LINES (sympathetic ganglia, chromaffin cells, etc):
  - enhanced production and/or release of chemical (olfactory) signals
  - enhanced reactivity to chemical (olfactory), tactile, and visual signals
  - morphofunctional changes in both adrenal medulla and cortex, i.e., cascade of neuroendocrine events
“Hypothalamic NGF release could also play a crucial role in linking the "emotional" status caused by a psychosocial stressor and the biological needs of the organism (and of its brain) to "remember" the events leading to an appropriate (or inappropriate) coping with the stressor itself” (p. 223)

Brigata Paracadutisti "Folgore"
ACTH AND NGF LEVELS IN THE BLOOD OF PARACHUTISTS BEFORE AND AFTER JUMPING

Aloe L. et al. (1994) Proc Natl Acad Sci USA
Changes in plasma nerve growth factor levels in older adults associated with chronic stress

Maria Hadjiconstantinou\textsuperscript{a,b}, Lynanne McGuire\textsuperscript{a}, Anne-Marie Duchemin\textsuperscript{a}, Bryon Laskowski\textsuperscript{c}, Janice Kiecolt-Glaser\textsuperscript{a,d}, Ronald Glaser\textsuperscript{c,d,e,*}

Nerve Growth Factor and Smoking Cessation

TO THE EDITOR: Nerve growth factor is the best characterized neurotrophin essential for neuron survival, differentiation, and function in the peripheral and central nervous systems (1). In addition, it is hypothesized that nerve growth factor plays a modulatory role in the immune system, is involved in the regulation of specific neuroendocrine functions, and is elevated in psychologically stressful situations (1). Because acute nicotine withdrawal is associated with psychological stress, and an elevation of nerve growth factor has been shown to accompany alcohol withdrawal (2), we hypothesized that the level of nerve growth factor is elevated during withdrawal from smoking.

UNDINE E. LANG, M.D.
JÜRGEN GALLINAT, M.D.
sILKE KUHN, M.A.
MARIA C. JOCKERS-SCHERÜBL, M.D.
RAINER HELLWEG, M.D.
Berlin, Germany
Passionate Love Scale

Table 1  Plasma neurotrophins concentrations in the three study groups.

<table>
<thead>
<tr>
<th></th>
<th>Subjects in love (n=58)</th>
<th>Long-lasting relationship (n=58)</th>
<th>Singles (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF (pg/ml)</td>
<td>227 (14)(^a)</td>
<td>123 (10)</td>
<td>149 (12)</td>
</tr>
<tr>
<td>BDNF (ng/ml)</td>
<td>11.3 (0.6)</td>
<td>11.6 (0.8)</td>
<td>11.7 (0.7)</td>
</tr>
<tr>
<td>NT-3 (pg/ml)</td>
<td>435 (23)</td>
<td>462 (24)</td>
<td>456 (25)</td>
</tr>
<tr>
<td>NT-4 (pg/ml)</td>
<td>42.1 (0.9)</td>
<td>44.3 (1.1)</td>
<td>45.1 (1.2)</td>
</tr>
</tbody>
</table>

Data are expressed as means (SEM).
\(^a\) p<0.001 versus both the comparison groups.

Romantic love induces an increase of circulating NGF (160-170% of basal levels) lasting about a year

Emanuele et al. Psychoneuroendocrinology 2006
LONG-TERM EFFECTS OF EARLY SOCIAL EXPERIENCE

- early social enrichment

  communal nesting

- adult social behaviour

  social/agonistic behaviour

- brain neurotrophin levels

  NGF and BDNF levels
MOTHER-OFFSPRING INTERACTION

The mother is the most pervasive, powerful and least understood source of early experience for the mammalian infant.

Basic physiological systems are regulated by the mother, including brain development.
MOTHER-OFFSPRING INTERACTION

- Licking and grooming
- Nursing
- Retrieving

Nelson, 1995
MOTHER-OFFSPRING INTERACTION

effects on physiology and behaviour of adult offspring
- Seymour ‘Gig’ Levine (University of Stanford)
- Michael Meaney (McGill University)

maternal behaviour of the female offspring
emotional response
coping response to stress
cognitive abilities?
social behaviour

Figure 13.9.2 Maternal behaviors: (A) retrieving; (B) nursing.

Capone, Bonsignore, and Cirulli, 2005, Current Protocols in Toxicology
EARLY MANIPULATION: COMMUNAL NESTING

Communal nesting (CN): three mothers keep their pups together in a single and share care-giving behaviour from birth to weaning (postnatal day 25)

compared to standard nesting laboratory condition (SN)
COMMUNAL NESTING: MATERNAL BEHAVIOUR

higher levels of maternal care were shown under CN

### = p < 0.001, CN vs. SN mice. n = 8 for each group. Data are means ± S.E.M

arched back nursing

Branchi et al, Biol Psychiatry, 2006
ADULT SOCIAL/AGGRESSIVE BEHAVIOUR

SN mice learn session after session to play their social role

ATTACK

Branchi et al, Biol Psychiatry, 2006
CN mice show higher social competencies, playing more promptly a social role.

** = $p < 0.01$ vs. the relative SN group (i.e., either dominants or subordinates)

Branchi et al, Biol Psychiatry, 2006
ADULT SOCIAL/AGGRESSIVE BEHAVIOUR

* and ** = respectively $p < 0.05$ and $< 0.01$ vs. the relative SN group (i.e., either dominants or subordinates); ### = respectively $p < 0.001$, CN vs. SN mice

Branchi et al, Biol Psychiatry, 2006
**ADULT SOCIAL BEHAVIOUR**

**CN mice display higher propensity to interact socially**

<table>
<thead>
<tr>
<th></th>
<th>SN</th>
<th>CN</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>allogrooming</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>freq</td>
<td>0.70 ± 0.40</td>
<td>7.65 ± 1.65</td>
<td>= 0.0001</td>
</tr>
<tr>
<td>dur (s)</td>
<td>2.00 ± 1.00</td>
<td>33.5 ± 7.4</td>
<td>= 0.0002</td>
</tr>
<tr>
<td><strong>nose sniffing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>freq</td>
<td>23.4 ± 3.00</td>
<td>31.65 ± 4.50</td>
<td>= 0.0044</td>
</tr>
<tr>
<td>dur (s)</td>
<td>50.05 ± 8.20</td>
<td>87.85 ± 15.00</td>
<td>= 0.0038</td>
</tr>
<tr>
<td><strong>anogenital sniffing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>freq</td>
<td>53.4 ± 5.65</td>
<td>87.1 ± 6.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>dur (s)</td>
<td>111.10 ± 16.75</td>
<td>200.00 ± 19.15</td>
<td>= 0.0597</td>
</tr>
</tbody>
</table>

*Table 1.* Propensity to social interaction changes according to early social experiences. CN mice showed higher levels of social investigation behaviors than SN mice. Data are mean ± S.E.M. n.s. = not statistically significant.

Branchi et al, Biol Psychiatry, 2006
NEUROTROPHIN LEVELS

Brain neurotrophin levels are modulated by early and/or adult social experiences.

* and ** = respectively $p < 0.01$ and $p < 0.001$ vs. SN mice. 
$$, $$ and $$$ = respectively $p < 0.05$, $p < 0.01$ and $p < 0.001$

vs. same nesting condition dominant mice. ## and ### = respectively $p < 0.01$ and $p < 0.001$.

Branchi et al, Biol Psychiatry, 2006
(SOCIAL) STRESS

↓

(SOCIAL) COPING

↓

RENEWED BRAIN PLASTICITY
ENHANCED VULNERABILITY TO DEPRESSION (MOOD DISORDERS)

“PARA”PHYSIOLOGICAL GROWTH FACTOR(S) LEVELS

NGF for what? BDNF for what?
PSYCHOSOCIAL STRESS INCREASES CIRCULATING NGF LEVELS


Recent Reviews


NGF, NEUROTROFINE E RIABILITAZIONE NEURO-MOTORIA: prospettive per una interazione tra l’Istituto Ortopedico Rizzoli e l’Istituto Superiore di Sanità