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¿REPRESENTAN LAS ENDORFINAS LA BASE BIOQUÍMICA DE LA HERENCIA DE LA INFORMACIÓN MENTAL?

DO ENDORPHINS REPRESENT THE BIOCHEMICAL BASIS OF INHERITANCE OF MENTAL INFORMATION?

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RESUMEN

En un artículo reciente (06/2009) Halabe Bucay presenta la hipótesis de que las endorfinas pueden ser un elemento clave en la transmisión a la siguiente generación de información mental producida a lo largo de la vida. Este artículo sostiene que el modelo de Bucay está basado en cuatro axiomas esenciales, sujetos a debate. El objetivo de este artículo es discutir esos axiomas específicos y evaluar la viabilidad de la hipótesis. Los axiomas específicos son: 1) "Las endorfinas actúan directamente en funciones espermáticas diferentes, lo que implica una influencia en la expresividad genética de las mismas", 2) Los opioides exógenos afectan los genes y éste puede ser un medio a través del cual se puede transmitir la información adquirida a la siguiente generación bajo la influencia de opioides endógenos; 3) La información mental producida a lo largo de la vida puede ser transmitida; 4) Las endorfinas están específicamente relacionadas con el presunto fenómeno, lo que justifica el marco epistemológico. Los cuatro axiomas son refutados por la mayoría (si no todos) de los estudios que abordan estos temas específicos, lo que nos lleva a concluir que dicha hipótesis no se sostiene. Al mismo tiempo, la hipótesis presenta una oportunidad única para discutir el papel de los neuropéptidos en el comportamiento y su posible rol en la constitución del cerebro. Al respecto, agregamos que es posible que los niveles de endorfinas en los entornos fetal y neonatal estén asociados con procesos epigenéticos (por ejemplo, la metilación) y tengan efectos a lo largo de toda la vida, —aunque no desarrollamos en profundidad esta idea por cuanto ello requeriría un enfoque totalmente diferente, basado en axiomas completamente distintos—.

Palabras clave: *genética, endorfinas, información mental.*

ABSTRACT

In a recent article (06/2009), Halabe Bucay presents the hypothesis that endorphins can be a core element in the transmission of mental information produced during life to the next generation. This

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paper argues that Bucay's model is based on four essential axioms, which are subject to debate. The aim of this paper is to discuss these specific axioms and evaluate the feasibility of the hypothesis. The specific axioms are: 1. "Endorphins act directly on different sperm function which implies their influence on the genetic expressivity of the same"; 2. Exogenous opioids affect genes and this could be a means through which acquired information could be transmitted to the next generations under the influence of endogenous opioids; 3. "Mental information produced through life" could be transmitted; 4. Endorphins are specifically related to the presumed phenomenon, thus justifying the epistemological frame. The four axioms are contested by most (if not all) studies addressing these specific issues which leads us to conclude that the hypothesis cannot be held. At the same time, the hypothesis presents a timely opportunity to discuss the role of neuropeptides on behavior and their possible role in the constitution of the brain, in regard to which we add that it is possible that endorphin levels within fetal and neonate milieus are associated with epigenic processes (e.g., methylations) and produce lifelong effects —although we do not develop this idea further, since it would require a totally different focus, based on completely different axioms—.

Keywords: *genetics, endorphins, mental information.*

In a recent paper published in the Journal Bioscience Hypotheses (Published by Elsevier), Alberto Bucay proposes that endorphins, which "participate in various mental processes", "act directly on different sperm function" and through the modification of the genetic expression of these cells "transmit the mental information produced through life to the next generations" (Bucay, 2009). This is a very bold hypothesis, not only in regard to what he proposes, but certainly in relation to what it assumes. In that sense, the purposes of this paper are to untangle these assumptions and, from that starting point, to discuss the feasibility of the hypothesis, and to introduce alternative ideas if that proves to be necessary.

WHAT ENDORPHINS ARE AND HOW THEY RELATE TO BEHAVIOR AND PERSONALITY?

Endorphins are alkaloids with analgesic properties that are synthesized from the precursors l-tyrosine and the methyl group of l-methionine through enzymatic activity (Poeaknapo, Schmidt, Brandsch, Drager & Zenk, 2004).

They are part of the group of signaling molecules known as neuropeptides and believed to be present in many human tissues, including tissues from the peripheral nervous system (PNS) and the central nervous system (CNS). There are three types of endorphins α-, β-, γ-; mass spectography from hypothalamic tissue revealed that the amino acid sequence for α- and γ- types respectively are: H-Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-OH– and H-Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-OH (Guillemin, Ling & Burgus, 1976); β-endorphin amino acid sequence is Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr- Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys- Asn-Ala-Tyr-Lys-Lys-Gly-Glu (Banks & Kastin, 1987); β-endorphin is a product of pro-opiomelanocortin (POMC).

Leaving aside the issue of pain relief, there are many other possible ways in which endorphins may contribute to the formation of the personality, but the canonical idea is that they take part in brain reward networks, which mediate nearly all consummatory behavior. In that sense, endorphins have been associated with drug seeking (Roth-Deri, Green-Sadan & Yadid, 2008), mood instability (Emrich, 1984), pathological gambling (Blaszczynski, Winter & McConaghy, 1986), major depression (Bernstein et al., 2002), Addison's disease (Anglin, Rosebush & Mazurek, 2006), schizophrenia (Berger, Watson & Akil, 1980), and many other behavioral dysfunctions and chronic disorders. At the same time, acute increase in these neuropeptide levels have been related to many types of euphoric behavior, including transient mania after ECT therapy (Chaudhry et al., 2000), over-training euphoria among athletes (Cunha, Ribeiro & Oliveira, 2008), and psycho-

logical reaction among bungee jumpers (Hennig, Laschefski & Opper, 1994). Moreover, one way of understanding the general influence of endorphins in normal behavior is related to the finding that beta-endorphins modulate behavioral responses to social conflict and control the release of cortisol (Vaanholt, Turek & Meerlo, 2003); for a review on recent findings: Bodnar (2007).

As these findings suggest, endorphins indeed "participate in various mental processes", some of which take part in disorders such as schizophrenia, major depression, drug addiction, which have been often associated with heredity –although not in a straightforward manner.

BUCAY'S FOUR EXCLUSIVE AXIOMS

In the previous section we discussed the role of endorphins in behaviors that are to an extent inherited. Now we will discuss four axioms belonging to the hypothesis, which we believe express its specificity. These are:

1. "Endorphins act directly on different sperm function which implies their influence on the genetic expressivity of the same".
2. Exogenous opioids affect genes and this could be a means through which acquired information could be transmitted to the next generations under the influence of endogenous opioids.
3. "Mental information produced through life" can be transmitted.
4. Endorphins are specifically related to the phenomenon under consideration, thus justifying the epistemological frame.

Axiom 1 (A-1): The article by Agirregoitia et al. (2006) that the author cites in regard to endorphins' effects on sperm function asserts that this topic is "incompletely understood and in some aspects is still controversial" (Agirregoitia et al., 2006, p. 4969) and addresses the possibility that the effect relates to sperm motility —which is an assumption based on the fact that opiate drug addicts show reduced sperm motility and the encephalin-metabolizing enzyme amino peptidase N is lower in males with asthenozoospermia— additionally, a possible role of endorphins in spermatogenesis is also raised.

Up to the current days, a modest number of studies have discussed whether sperm motility could alter the chromosomes —thus suggesting that this question needs to be explored further— but it is a fact that all findings to date have been negative (e.g., Benet, Genesca, Navarro, Egozcue & Templado, 1992; Samura, Miharu, He, Okamoto & Ohama, 1997). We also searched for papers specifically addressing the relation between endorphins' effects on sperm function and their influence on the DNA, but we did not find any paper presenting experimental proof of that in Pubmed, although we did find the opposite, e.g.: "There was no correlation between β-endorphin concentration and sperm characteristics" (Zalata, Hafez, Van Hoecke & Comhaire, 1995; for further discussion on the relation defined by endorphins and sperm: Agirregoitia et al., 2006; Fabbri et al., 1989; Graczykowski, Vermesh, Siegel, Davidson & Lobo, 1990).

Notably, this perspective seems to contradict findings suggesting genomic effects of opioid addiction (e.g., Rodríguez Parkitna et al., 2004). Nevertheless, this first impression does not hold: in first place, molecular cascades through which morphine and endorphin act in the body are not the same (Suh, Tseng & Li, 1988; Tseng & Suh, 1989; Tseng & Tang, 1990) even when the phenomenological output is identical (Tseng & Tang, 1990); as a matter of fact, they even show opposite interactions with certain chemicals (Smith, Robertson & Monroe, 1992). Secondly, as one study suggests, morphine administered to one-day-old rats is incorporated into brain DNA but the effect cannot be replicated by endogenous opioids (Hennig et al., 1994).

In conclusion, A-1 does not hold, despite the fact that endorphins exert a role in spermatic function and morphine intake can affect the DNA.

Axiom-2 (A-2): In relation to the suggestion that endorphins may represent a key to our understanding of the transmission of acquired traits, the author states that:

"Mental processes that comprise our personality throughout the whole of our lives, manifested, among others, from the release of endorphins, send this biochemical information to the sperm and spermatogonial cells in the person,

just as opioid drugs and marijuana, which alter this genetic expressivity; these endorphins modify the genetic expression of the germinal cells (…) to transmit the mental information produced through life to the next generations.

As the statement reveals, the author assumes that complex information (mental information) can be transmitted in this fashion. Moreover, it seems to me that he also assumes the continuity between molecular cascades involving endorphins in the brain and in reproductive cells, although it is not possible to verify that.

In relation to this last point, although it is currently believed that peptides can cross the blood brain barrier (BBB), the literature on this matter indexed in Pubmed shows that either endorphins cannot pass through the BBB or they can pass only in miniscule amounts; e.g.: "Studies in non-human primates suggest that systemically administered b-endorphin is unable to produce centrally mediated effects, presumably due to pharmacokinetic factors, including difficulty in crossing the blood-brain barrier" (Butelman et al., 2008, p. 293). Using a data mining tool, we also searched Web of Science for papers of interest and could not find a single study providing experimental evidence that considerable amounts of endorphins could pass through the BBB, while it is also important to note that the canonical pathway is → brain, not the opposite.

In relation to the former —and most important— point, the conventional approach holds that genes transmit information while opioids and other drugs of abuse that may affect DNA (such as LSD) increase perturbation, which is exactly the opposite. In other words, the effects on genes caused by drugs of abuse cannot possibly contribute to synthesize a new and complex structure, as in the case of mental information produced during life, but only to increase the chance of random mutations or disruptions of the synthesis of predefined compounds, which mainly occurs through the alteration of the concentration of transcription factors in the nuclei of certain cells (Rhodes & Crabbe, 2005).

There is a questionable step in the author's assertion that: "just as opioid drugs and marijuana, which alter this genetic expressivity; these endorphins modify the genetic expression of the germinal cells (…) to transmit the mental information produced through life to the next generations". Here the author draws a parallel between mental content in the mind and mental content in the next generations, and drugs of abuse and their effects on the next generations. If this parallel holds, one would expect that if a person without any specific genetic tendencies toward drug abuse used heroin to the extent that this affected his/her DNA, the transmission of a specific tendency to use heroin would then follow; on the contrary, there is no evidence supporting this idea.

As in the case of mental content produced during life, drugs of abuse cannot introduce precise and organized information in the genome, to be expressed in the following generation. This idea reproduces Lamarck's most notable conception, which has been exhaustively discussed and generally discredited over the last two centuries, despite emerging proof of the transmission of acquired characteristics, some of which associated with environmentally-induced effects on neural tissues (Drosophila) (Sharma & Singh, 2009).

Moreover, the author states that transmission would be guided by effects on "genetic expressivity". The concept of genetic expressivity is used to characterize the extent to which a gene is expressed in an individual or group or, in other words, the degree of allelic expression of a penetrant allele (e.g., a mutation that normally leads to a two-fold increase in the number of X can be restricted to an X/3 increase in a certain individual, which shows reduced genetic expressivity). In that sense, the concept is unrelated to the transmission of any kind of new information to the next generation.

An alternative hypothesis with great chances of future experimental support is that epigenic processes influence the release of endorphins in fetuses and neonates, affecting the development of certain neuroanatomical and neurophysiological traits and distorting behavioral tendencies. If this proves to be the case, it may also suggest that this effect relates to post-replication modification in CpG's cytosines (methylations), which are known to modify the expression of genes (Jaenisch & Bird, 2003) and have been associated

with developmental instabilities affecting neural tissues (Flight, 2007).

Epigenic abnormalities have been linked to several mental disorders (for a review: Stuffrein-Roberts, Joyce & Kennedy, 2008), among which schizophrenia is the most prominent (201 publications indexed in Pubmed in 07/2009); recently it has been suggested that this effect would be present mainly in association with the synthesis of the GABA-ergic neurons, which express high levels of DNA-methyltransferase-1 (Costa et al., 2007). Our suggestion for future research is to explore whether this effect also relates to neuropeptides. It should be noted that not a single study indexed in Pubmed tests this association, thus suggesting that, as of yet, the lack of evidence seems to reflect a lack of studies on the matter.

Furthermore, prenatal stress increases chances of maladaptive behavioral stress responsivity, anhedonia, long-term alterations in central corticotrophin-releasing factor, among other disorders (Mueller & Bale, 2008), and seems to dialogue with the hypothesis. However, one should note that these effects are associated with a specific time-window (early pregnancy), are gender specific (mainly influenced by the mother, mainly affecting males) and, most of all, affect basic brain circuits, without reaching the level of mental content directly.

In conclusion, A-2 contradicts basis assumptions about hereditability and neurochemistry within the Homo sapiens milieu and thus does not hold, while alternative hypotheses should be explored further.

Axiom 3 (A-3): One of Bucay's most controversial ideas relates to the object of transmission under focus: the long-held idea that "mental information produced through life (could be transmitted) to the next generations". So far, there is no experimental evidence supporting the transmission of mental information produced during life and it is reasonable to assume that this situation will not change so soon. The case for such a lack of evidence directly relates to the fact that mental information produced during life is determined by the distribution of the synaptic weight within the ≈ 100 trillion synapses that compose the connectivity tissue of the brain (for a discussion regarding both symbolic and connectionist approaches to this scientific canon: Marcus, 2001).

Despite the fact that long term memories imply the synthesis of new proteins —both in relation to psychological traumas (Schore, 2001) and non-affective long term memory (Kandel, Schwartz & Jessell, 2000)— this is not a two way street, after all, the indeterminacy offered by synaptic plasticity is ultimately related to adaptations to complex environments and the costs of carrying all that information in the genome would overcome its benefits in every possible sense.

Finally, mental information does not establish a direct relation with the synthesis of any group of proteins and thus cannot be approached in the way proposed by Bucay – or from the hypothesis that endorphins produce epigenic effects, for that matter.

In conclusion, A-3 assumes a problematic approach to the relation between genes and mental information produced through life and thus the axiom does not hold.

Axion 4 (A-4): The final axiom to be discussed involves the reasons to specifically focus on endorphins. It is important to note that dopaminergic receptors have also been found in the sperm of many mammals (Mogensen, Kinze, Werge & Rasmussen, 2006; Otth et al., 2007; Ramírez et al., 2009), mainly in association with the same function that is exerted by opioid receptors: regulation of spermatic locomotion (Ramírez et al., 2009). On the other hand, dopamine has been very strongly related to general patterns of behavior (especially in regard to rewards and error prediction) and psychiatric disorders. Finally, it is important to note that the same can be applied to serotonin.

In conclusion, there is nothing specific in relation to endorphins that might justify the epistemological frame defined by the focus on these neuropeptides, thus leading to the perspective that A-4 also does not hold. If it was the case to consider the effects of mental content on spermatic function in depth, it would be better to approach it from the perspective of a combined neurochemical effect.

FINAL REMARKS

The hypothesis that endorphins represent a biochemical base of inheritance of mental information produced during life does not hold, although it introduces instigating perspectives. Opioids are underrepresented in the literature and should be explored further; and they certainly display very interesting (and mostly unknown) characteristics, among which some related to personality and others could be involved in epigenic processes. It would be very interesting to have an increasingly clear picture of these issues and Bucay's initiative certainly contributes to the development of that debate.

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