Medical Hypotheses 77 (2011) 685–691

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Startle response related genes

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ARTICLE INFO

Article history:
Received 29 April 2011
Accepted 7 July 2011

ABSTRACT

The startle reaction (also known as the startle response, the startle reflex, or the alarm reaction) is the psychological and physiological response to a sudden unexpected stimulus, such as a flash of light, a loud noise (acoustic startle reflex), or a quick movement near the face. Abnormalities of startle response have been observed in many stress-related mental disorders, such as schizophrenia and post-traumatic stress disorder (PTSD). However, the molecular mechanisms of startle in stress-associated conditions – for example, whether the startle reaction is associated with any gene variance – is still unknown. In this paper, we will carry out a systematic review by retrieving, assessing, and combining, when applicable, individual studies investigating association of the molecular variation of candidate gene with the startle response. The systematic review is based on the search for numerous publications using the keywords "startle gene" on September 15, 2010 using PubMed, which comprises more than 20 million citations for biomedical literature from MEDLINE and life science journals. A total of 486 publications regarding genes associated with startle have been obtained and reviewed here. There are fewer than 20 publications associating genes with the startle response between 1979, when the first valuable paper was published, and 1999. However, publications have dramatically increase from 2001 and reaches over 70 in 2009. We have characterized them into three categories: startle-associated gene studies in humans, in animals, as well as in both human and animals. This review of research strategy may provide the information for identifying a biomarker for startle response, with the objective of translating research into clinical utility: diagnosis and treatment of stress-induced mental disorders.

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Introduction

An exaggerated startle response, considered as a critical characteristic in certain mental disorders, such as PTSD and schizophrenia, has been avidly studied in psychiatry. Research seeking the molecular mechanism of the startle response has consistently increased over last 10 years. One such area of research is the study of genes associated with the startle response. The published articles about startle response associated genes have been significantly increased yearly. As a phenotype, the startle response exhibits a consistent physiological pattern including physical movement away from a given stimulus, a contraction of the muscles of the arms and legs, blinking, and changes of blood pressure, respiration, and breathing rate. The muscle reactions generally resolve themselves in a matter of seconds, while other responses may take longer. The pathway for this response was largely elucidated in rats in the 1980s [1].

The basic neuroanatomy, which is demonstrated by experiments with rats using a variety of lesion and electrical stimulation procedures, is relatively simple for startle responses. The signals are conducted to the central nervous system. The output end of the startle circuitry goes through the reticulospinal tract and the lower motor neurons of the spinal cord. For example, the pathway for acoustic startle is from the ear up to the nucleus of the lateral lemniscus (LLN) from where it then activates a motor center in the reticular formation. LLN sends descending projections to lower motor neurons of the limbs. The whole reflex takes place in less than 10 ms [2]. Accordingly, the human startle response can be measured reliably. For example, it can be measured by the amplitude of eye blinking in response to a sudden abrupt auditory stimulus [3]. Besides the above control circuitry, the startle circuit is regulated by several brain regions, such as the prefrontal cortex and amygdala, which influence the tone of startle and the processing of information related to conditional fear [4], respectively.

There are two typical examples for regulation of the startle response. First, is prepulse inhibition (PPI). PPI is a neurological phenomenon in which a weaker pre-stimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse) [5]. The reduction of the amplitude of startle reflects that the nervous system temporarily adapts to a strong sensory stimulus when a preceding weaker warning signal is given. PPI deficits are noted in patients with schizophrenia [6–9] and Alzheimer's disease, and in people under the influence of drugs, surgical manipulations, or gene mutations.

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0306-9877/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.mehy.2011.07.018

The second example for regulation of the startle response is startle habituation. Startle response can be decremented by repeated presentation of the same, initially novel stimulus [10]. This regulatory mechanism can be inhibited. Schizophrenia patients exhibit impairment of startle habituation. In general, exaggerated startle reactivity can become a chronic condition to lasting for 30, 40, or more years [11].

If human behavioral traits result from the interplay of genes and environment, exaggerated startle response may have a complex genetic basis. Although it is not necessarily inherited in strict Mendelian fashion, the transmission of hereditary characteristics does pass from parents to offspring. Factors such as incomplete penetrance – (carriers of the disease allele not becoming ill or having a later onset), pleiotropy (multiple effects of a single gene), heterogeneity (similar phenotype from different genotypes), epistasis (interaction of multiple alleles in the same subject) and epigenetics among others, must be accounted for. Since startle is a peculiar behavioral response to stimuli, it represents an excellent model for studying the mechanism of interaction of gene and environment. We hypothesize that startle is an endophenotype (a concept which divides behavioral symptoms into stable phenotypes with a clear genetic connection – seen in mental disorders, such as schizophrenia and PTSD). It is possible to identify a gene, which is associated with startle response in a specific environment, for example, in subjects who experiences the Iraq war and in a restrictive population, such as military subjects. Those environmental factors, such as war exposure and subjects, can be defined. The determination of which genes are associated with startle response is a challenge.

There are 486 publications regarding gene and startle response. Fewer than 20 of these were published between 1979 and 1999. The total numbers of publications have increased markedly since 2001, reaching over 70 publications in 2009. Depending on the research subjects, they can be categorized into: studies in human subjects (Table 1), studies in animals (Table 2) and studies in both human and animals. There are 13 genes which are associated with startle response in human studies. Four genes have been studied in both human and animals, including COMT, GLRA1, GlyT2, and NRG1 dehydrogenase. Here we briefly discuss several genes which are associated with startle response in both humans and animals, and in psychiatric researches.

The 5-HT transporter (5-HTT) and startle response

There are studies regarding 5-HTTLPR (serotonin-transporter-linked promoter region) and startle-related topics. 5-HTTLPR is a degenerate repeat polymorphic region in *SLC6A4*, the gene that codes for the serotonin transporter [30,31] and is associated with many neuropsychiatric disorders [32]. The 5-HT transporter (5-HTT) influences on neural circuits processing fear and anxiety are discussed [33]. 5-HTTLPR, a functional polymorphism of the 5′-flanking region of the 5-HTT gene is involved in several neuropsychiatric phenotypes [34]). 5-HTTLPR is an insertion/deletion polymorphism with a long (L) variant comprising 16 copies of a 20–23 bp repeat sequence and a short (S) variant comprising 14 copies. Among Caucasians, the frequencies of the L and S alleles are about 0.60, and 0.40, respectively [35]. An association study regarding 5-HTT, especially the S allele with anxiety, fear and startle response has been studied in human subjects (Table 1). The S allele is associated not only with increased scores in measures of negative emotionality including anxiety [36–38], but also with lower transcriptional efficiency of the 5-HTT gene and lower levels of 5-HT uptake [30,35]. S allele carriers show stronger amygdala activity in response to fear stimuli than L/L homozygotes [33] and increased anxiety [39,40]. The S allele is also specifically associated with stronger overall startle responses than L/L homozygotes [41]. S allele carriers were not only more sensitive to the effects of stressful life events than L/L homozygotes, but also were more likely to develop depressive symptoms [42–47]. S allele carriers with low social support had an increased risk for behavioral inhibition, indicating that in the early years of life before maturation of prefrontal regulatory circuits, stress could produce stronger response to fearful stimuli. In addition, stressful life events may have cumulative effects [42,45]. However, there is a negative result in the study of the relation of 5-HTTLPR with fear and anxiety [45]. No interaction of 5-HTTLPR and stressful life events was found on the risk for generalized anxiety disorder in adults, although the positive results demonstrated an interaction of 5-HTTLPR and environment on fear and anxiety in children.

COMT genetic variation and startle response

One of the promising, well-studied candidates for the association of gene with startle is the gene for catechol-O-methyltransferase (COMT), the catabolic enzyme for dopamine, norepinephrine, and epinephrine. COMT is the major clearing step for dopamine in the prefrontal cortex [48,49] and expressed in many brain regions synaptically [50,51] and subcortically [52]. The COMT gene contains a common functional polymorphism resulting from a non synonymous G to A base pair substitution in the coding sequence of the gene, producing a valine to methionine substitution at position 158 of the membrane bound allozyme that predominates in the brain (MB-COMT); soluble allozyme S-COMT [53]. Since the

Table 1
Startle associated gene studies in human subjects.

Gene	Location	Polymorphism	Phenotype	References
5-HT(2A)R	13q14-q21	A-1438 G and T102C	PPI	[12,13]
		T102C	PPI	[14]
AVPR1a	12q14-15	VNTR (RS1 and RS3)	PPI	[15]
AADC	7p12.2	1303 C > T 1367ins A	Startle	[16,17]
COMT*	22q11.21	Val158Met	PPI	[18]
CSF1-R*	5q32	D5S209, and D5S119	Hyperekplexia	[19,20]
DRD3	3q13.3	Ser9Gly	PPI	[21]
DRD4	11p15.5	7-folds repeat	Startle	[22]
GLRA1*	5q32	Arginine271proline	Hyperekplexia	[23]
GlyT2*	11p15.1	Arg271Pro	Hyperekplexia	[20]
		910A>C/Lys304Gln	Hyperekplexia	[24]
HTTLPR	17q11.2	S/L	Startle	[25,26]
NRG1*	8p12	rs3924999/rs10503929	PPI	[27]
PRODH	22q11.21	1945T/C, 1766A/G, 1852G/A	PPI	[28]
TPH2	11p15.3-p14	−703G/T	Startle	[29]

* Study in both human and animals. COMT, catechol-O-methyl-transferase; HTTLPR, serotonin-transporter-linked promoter region; TPH2, tryptophan hydroxylase 2.